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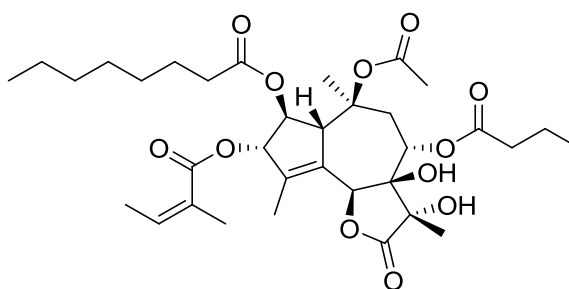
University
of Glasgow

Towards the Total Synthesis of Thapsigargin

Alan Jeuken

MChem

A thesis submitted in part fulfilment of the requirements of the degree
of Doctor of Philosophy



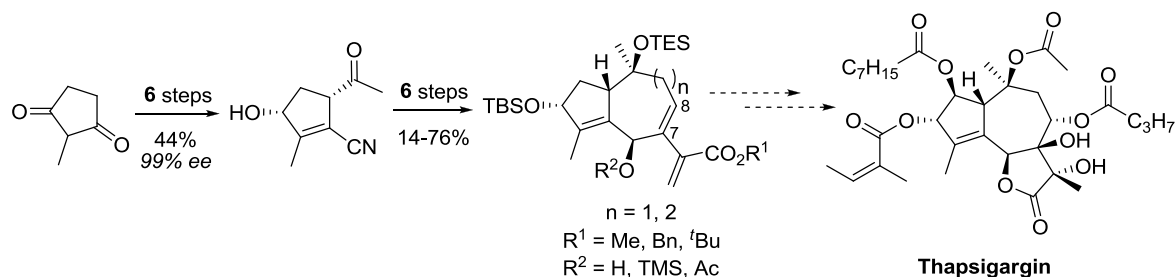
Thapsigargin

School of Chemistry
College of Science & Engineering
University of Glasgow

February 2019

*"There... are... **four**... lights!"*

Abstract



Thapsigargin is a sesquiterpene lactone of the guaianolide class whose structure was first assigned in 1984. It is a highly cytotoxic agent, inhibiting the sarco/endoplasmic Ca^{2+} -ATPase (SERCA) at sub-nanomolar concentrations ($K_D = 0.4 \text{ nM}$), and its prodrug formulations have been of intense interests for many oncological applications.

In collaboration with the group of J.-P. F  r  zou, a strategy towards the construction of the carbon skeleton of thapsigargin and related natural and unnatural analogues was developed based on a ring-closing ene-yne metathesis (RCEYM) step. In this work the scope of that strategy was expanded to fulfil the enantioselectivity requirement of the synthesis *via* the use of asymmetric transfer hydrogenation under dynamic kinetic resolution conditions on a cyclopentenone γ -ester. These enantioenriched cyclopentenone derivatives have then been used to construct [5,7]-bicyclic structures with varying substitutions.

These resulting bicyclic derivatives were sensitive to many subsequent reaction conditions, however a robust synthetic strategy was found to chemoselectively oxidise the C-7/8 double bond and from there further derivation was possible, resulting in an advanced [5,7,5]-tricyclic derivative.

Finally, the flexibility of the RCEYM strategy was demonstrated through the concise synthesis of an unnatural [5,8]-bicyclic thapsigargin core analogue from a common ketone precursor.

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Author's declaration

Name: **Alan Jeuken**

I certify that the thesis presented here for examination for a PhD degree of the University of Glasgow is solely my own work other than where I have clearly indicated that it is the work of others and that the thesis has not been edited by a third party beyond what is permitted by the University's PGR Code of Practice.

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Abbreviations list

Ac	Acetyl
acac	Acetylacetonate
AD	Asymmetric dihydroxylation
ADP	Adenosine diphosphate
Ar	Aryl
ATH	Asymmetric transfer hydrogenation
ATP	Adenosine triphosphate
BINAP	2,2'- <i>bis</i> (Diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CBS	Corey-Bakshi-Shibata
CDI	Carbonyldiimidazole
CEYM	Cross ene-yne metathesis
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DMAPP	Dimethylallyl pyrophosphate
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dpm	Dipivaloylmethane
dr	Diastereomeric ratio
ee	Enantiomeric excess
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionization

Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
FPP	Farnesyl diphosphate
HG II	Hoveyda-Grubbs 2nd generation catalyst
HMDS	Hexamethyldisilazane
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
HPLC	High performance liquid chromatography
IBX	2-Iodoxybenzoic acid
Im	Imidazole
IPP	3-Isopentenyl pyrophosphate
IR	Infrared Spectroscopy
LDA	Lithium diisopropylamide
MAD	Mevalonate-dependant
Me	Methyl
Mes	Mesityl
MO	Molecular orbital
MOM	Methoxymethyl
MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	<i>N</i> -Bromosuccinimide
NCI	National Cancer Institute
NHC	<i>N</i> -Heterocyclic carbene
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Nu	Nucleophile
OPP	Pyrophosphate
Ph	Phenyl
PMB	<i>p</i> -Methoxy benzyl
ppm	Parts per million
PPTS	Pyridinium <i>p</i> -toluenesulfonate
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
PTSA	<i>p</i> -Toluenesulfonic acid
Pr	Propyl

quant	Quantitative
RCEYM	Ring-closing enyne metathesis
RYR	Ryanodine receptors
SAR	Structure-activity relationship
SEM	(2-(Trimethylsilyl)ethoxy)methyl
SERCA	Sarco/endoplasmic reticulum Ca^{2+} ATPase
SR	Sarcoplasmic reticulum
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>t</i> -Butyldiphenylsilyl
TBS	<i>t</i> -Butyldimethylsilyl
TEG	Triethylene glycol
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
Tg	Thapsigargin
THF	Tetrahydrofuran
THP	2-Tetrahydropyranyl
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilane
Tol	Tolyl
TPAP	Tetra- <i>n</i> -propylammonium perruthenate
TsDPEN	<i>N-p</i> -Tosyl-1,2-diphenyl-1,2-ethylenediamine

Chapter 1: Introduction

1.1 Terpenoids

Terpenoids are the largest class of natural products found in living organisms.¹ The functional role of many of the approx. 25,000 discovered terpenoids² have yet to be investigated. Of particular interest are the relatively small (< 1 kDa), biologically active terpenoid natural products, as they allow for simpler derivatisation, structural elucidation and total synthesis as well as providing a general improvement in druglikeness.³

Sesquiterpene lactones are a large class of over 5000 known compounds⁴ with most of these found in quite prolific plant species. These terpenoids are constructed biosynthetically from three isoprene units and contain a γ -lactone ring, with varying oxidation levels around the core structure. Although a large number of sesquiterpene lactones are considered toxic at levels found in plants,⁵ dose regulation reveals the therapeutic potential of many compounds, and one area of particular interest is anti-cancer activity.⁶ Among those under investigation are the more well known thapsigargin **1** (Tg), helenalin **2** and artemisinin **3** (Figure 1).

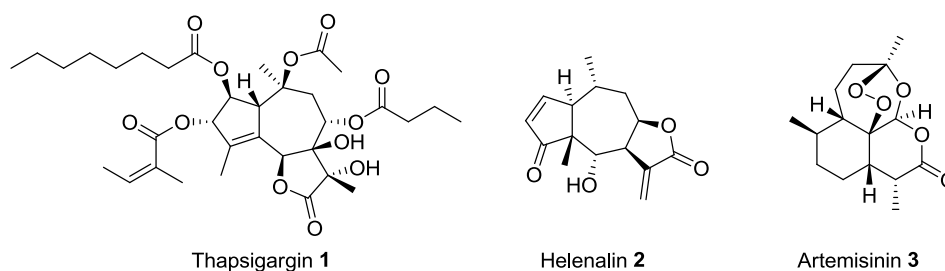


Figure 1. Three sesquiterpene lactone anti-cancer candidates.

Although they are structurally related, the mechanisms of their anti-cancer activity differ significantly. Thapsigargin **1** is a potent inhibitor of sarco/endoplasmic reticulum Ca^{2+}

¹ Gershenzon, J.; Dudareva N. *Nat. Chem. Bio.* **2007**, 3, 408.

² Buckingham, J. "Dictionary of Natural Products" **1994**, Chapman and Hall.

³ Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, 43, 218.

⁴ Wedge, D. E.; Galindo, J. C. G.; Macías, F. A. *Phytochemistry* **2000**, 53, 747.

⁵ Amorim, M. H.; Gil da Costa, R. M.; Lopes, C.; Bastos, M. M. *Crit. Rev. Toxicol.* **2013**, 43, 559.

⁶ Zhang, H.; Won, Y.-K.; Ong, C.-N.; Shen, H.-M. *Curr. Med. Chem. – Anti-cancer Agents* **2005**, 5, 239.

ATPase (SERCA), which regulates the flow of Ca^{2+} ions from the cytosol of the cell back to storage, leading to a Ca^{2+} flow disruption and eventual apoptosis.⁷ Helenalin **2** on the other hand impairs DNA and protein synthesis, significantly affecting the growth of tumours.^{8,9} While thapsigargin and helenalin are also very cytotoxic against healthy cells,^{10,11} artemisinin **3** is well tolerated in humans at clinically relevant doses as its mechanism of action utilises its unusual peroxide bridge to induce oxidative stress in typically iron-rich cancer cells.¹²

1.2 Terpenoid biosynthesis

1.2.1 Terpenoid precursors

All terpenoids are constructed from one or more isoprene units. 3-Isopentenyl pyrophosphate **4** (IPP) and dimethylallyl pyrophosphate **5** (DMAPP) are the two building blocks used to make larger and more complicated terpenoids. IPP **4** and DMAPP **5** are isomeric, and are made *via* the same pathways. Most eukaryotes, archaea and some bacteria utilise a pathway named the mevalonate-dependant (MAD) or HMG-CoA reductase pathway (Scheme 1).¹³

⁷ Drew, D. P.; Krichau, N.; Reichwald, K.; Simonson, H. T. *Phytochemistry Rev.* **2009**, *8*, 581.

⁸ Berges, C.; Fuchs, D.; Opelz, G.; Daniel, V.; Naujokat, C. *Mol. Immunol.* **2009**, *46*, 2892.

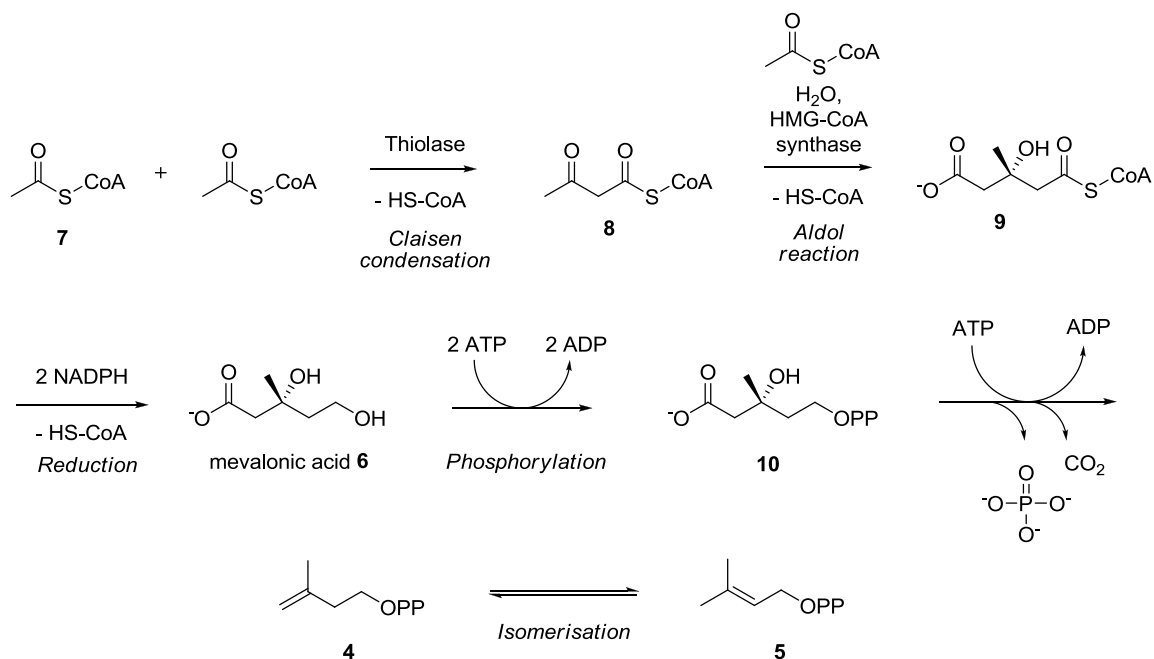
⁹ Lim, C. B.; Fu, P. Y.; Ky, N.; Zhu, H. S.; Feng, X.; Li, J.; Srinivasan, K. G.; Hamza, M. S.; Zhao, Y. *BMC Complement. Altern. Med.* **2012**, *12*, 93.

¹⁰ Ganley, I. G.; Wong, P.-M.; Gammoh, N.; Jiang, X. *Mol. Cell.* **2011**, *42*, 731.

¹¹ Chapman, D. E.; Roberts, G. B.; Reynolds, D. J.; Grippo, A. A.; Holbrook, D. J.; Hall, I. H.; Chaney, S. G.; Chang, J.; Lee K. H. *Tox. Sci.* **1988**, *10*, 302.

¹² Cabello, C. M.; Lamore, S. D.; Bair, III W. B.; Qiao, S.; Azimian, S.; Lesson, J. L.; Wondrak, G. T. *Investigational New Drugs* **2012**, *30*, 1289.

¹³ a) Beytía, E. D.; Porter, J. W. *Annu. Rev. Biochem.* **1976**, *45*, 113. b) Goldstein, J. L.; Brown, M. S. *Nature* **1990**, *343*, 425.



Scheme 1. Biosynthetic pathway leading to IPP and DMAPP

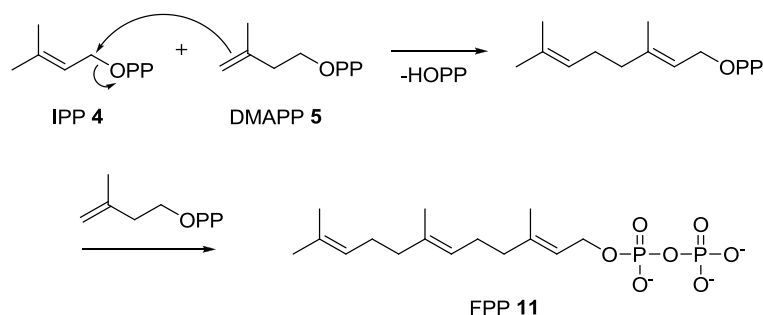
First, the formation of mevalonic acid **6** is accomplished through the Claisen condensation of acetyl-CoA **7** catalysed by thiolase and subsequent aldol reaction with **8**, followed by reduction of **9** using two equivalents of nicotinamide adenine dinucleotide phosphate (NADPH). It is then phosphorylated twice to form **10**. A final phosphorylation using adenosine triphosphate (ATP) then dehydrates and decarboxylates **10** to produce IPP **4**, which can undergo isomerisation to DMAPP **5**. An alternative biosynthetic pathway to IPP and DMAPP also exists in most bacteria, certain protozoa and in the plastids of higher plants.¹⁴

1.2.2 Guaianolides and pseudoguaianolides

Thapsigargin and helenalin belong to the sesquiterpene lactone subclasses of guaianolides and pseudoguaianolides respectively. Like all sesquiterpenoids, the guaianolide and pseudoguaianolide biosynthetic pathways originate from farnesyl pyrophosphate **11** (FPP),¹⁵ which in turn is made from 3-isopentenyl pyrophosphate **4** (IPP) and dimethylallyl pyrophosphate **5** (DMAPP) (Scheme 2).

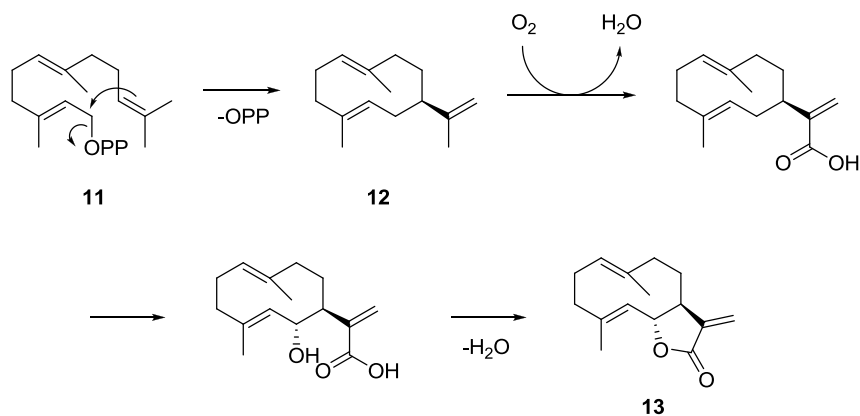
¹⁴ Lichtenthaler, H. K.; Schwender, J.; Disch, A.; Rohmer, M. *FEBS Lett.* **1997**, *400*, 271.

¹⁵ Bohlmann, J.; Meyer-Gauen, G.; Croteau, R. *Proc. Natl. Acad. Sci.* **1998** *95*, 4126.



Scheme 2. Sesquiterpene lactone precursor FPP biosynthesis from IPP and DMAPP.

The biosyntheses of guaianolides and pseudoguaianolides share much of the same route, and only diverge in later stages.¹⁶ As a general route, first FPP **11** undergoes direct cyclisation to macrocycle **12**, which is then oxidised, hydroxylated and lactonised^{17,18} to **13** (Scheme 3).



Scheme 3. Guaianolide biosynthesis.

The second part of the biosynthesis in Apiaceae is thought to utilise an epoxidation of **13**, followed by an intramolecular nucleophilic attack (Scheme 4).^{17,19,20} Depending on the enzymes involved, both 4,5 and 1,10-epoxidation are possible.²¹ At this point, the route to guaianolides and pseudoguaianolides diverge; α -proton elimination in **14** and **15** will lead to double bond formation and the guaianolide core structures of **16** and **17**. However, a

¹⁶ Albrecht, L.; Albrecht, A.; Janecki, T. “*Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*” **2013**, Wiley, 147.

¹⁷ De Kraker, J. W.; Franssen, M. C. R.; Joerink, M.; de Groot, A.; Bouwmeester, H. J. *Plant Physiol.* **2002**, *129*, 257.

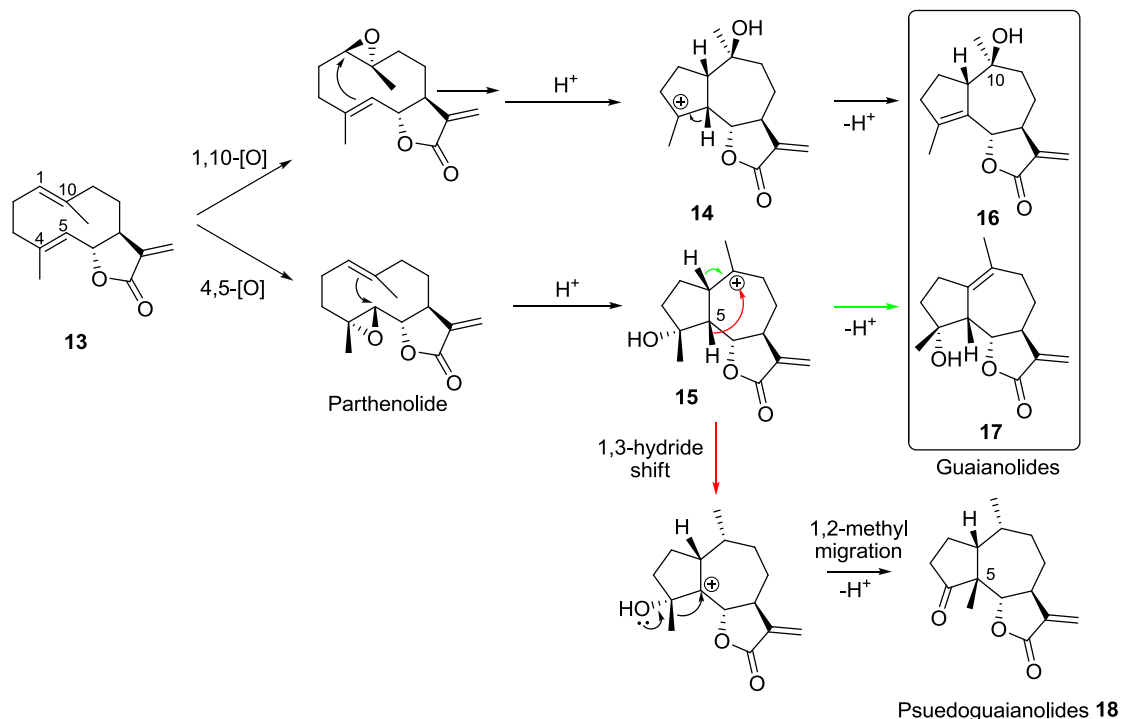
¹⁸ Ikezawa, N.; Göpfert, J. C.; Nguyen, D. T.; Kim, S.-U.; O'Maille, P. E.; Spring, O.; Ro, D.-K. *J. Biol. Chem.* **2011**, *286*, 21601.

¹⁹ Bouwmeester, H. J.; Kodde, J.; Verstappen, F. W. A.; Altug, I. G.; De Kraker, J. W.; Wallaart, T. E. *Plant Physiol.* **2002**, *129*, 134.

²⁰ Dewick, P. M. *Nat. Prod. Rep.* **1995**, *12*, 507.

²¹ Song, Q.; Gomez-Barrios, M. L.; Hopper, E. L.; Hjortso, M. A.; Fischer, N. H. *Phytochemistry* **1995**, *40*, 1659.

formal 1,3-hydride shift followed by a 1,2-methyl migration to the 5-position on **15** will result in the closely related pseudoguaianolide structure **18**. Many rearrangement reactions are of course possible, and lead to a wide variety of other sesquiterpene lactones.



Scheme 4. Biosynthetic route to both guaianolides and pseudoguaianolides.

1.2.2 Thapsigargin

Thapsigargin **1** is a highly oxygenated guaianolide whose structure was first elucidated in 1984 by Christensen.²² It is found in the Mediterranean plant *Thapsia garganica*, part of the Apiaceae family, and has been used in local herbal medicine for centuries to combat rheumatic pain. Structurally it contains a γ -lactone, four ester groups, two free hydroxyl groups and a total of eight stereogenic centres, three of which are fully substituted, all attached to the core [5,7,5] tricycle (Figure 2).

²² a) Christensen, S. B.; Norup, E.; Rasmussen, U.; Madsen, J. Ø. *Phytochemistry* **1984**, 23, 1659. b) Christensen, S. B.; Norup, E. *Tetrahedron Lett.* **1985**, 26, 107.

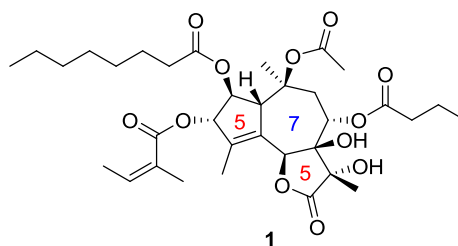
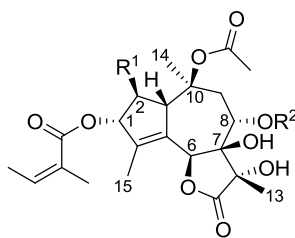


Figure 2. Thapsigargin.

Sixteen other thapsigargin-like molecules have also been isolated alongside thapsigargin from species in the Apiaceae family, and are included in Table 1. They differ only in the substituents attached to the C-2 and C-8 positions. Throughout this report, the thapsigargin numbering system will be used to indicate the corresponding skeletal carbons in thapsigargin.

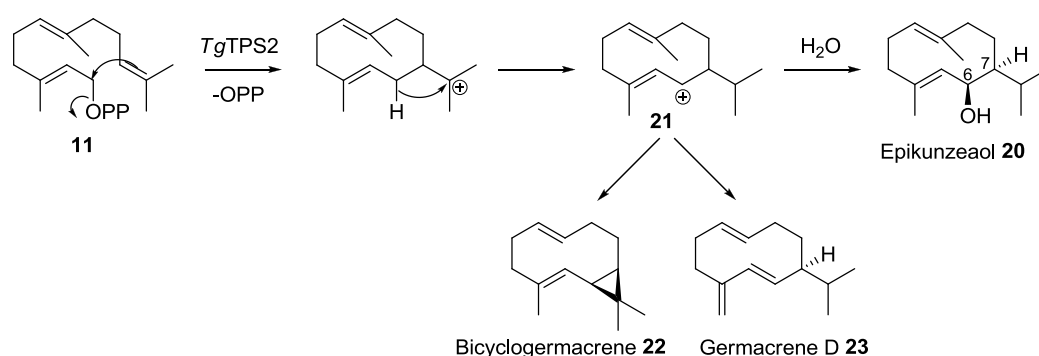
Table 1. The thapsigargin family.



Entry	Name	R ¹	R ²
1	thapsigargin	O-Oct	But
2	trilobolide	H	(S)-2-MeBut
3	nortrilobolide (19)	H	But
4	thapsivillosin F	H	Sen
5	thapsivillosin C	O-Oct	2-MeBut
6	thapsigargincin	O-Hex	But
7	thapsitranstagin	O- <i>i</i> Val	2-MeBut
8	thapsivillosin A	O-Ang	Sen
9	thapsivillosin B	O-Ang	2-MeBut
10	thapsivillosin D	O-6-MeOct	Sen
11	thapsivillosin E	O-6-MeOct	2-MeBut
12	thapsivillosin	O-6-MeHept	2-MeBut
13	thapsivillosin H	O-Ang or -Sen	Ang or Sen
14	thapsivillosin I	O-Ang	But
15	thapsivillosin J	O- <i>i</i> Val	But
16	thapsivillosin L	O-But	But
17	thapsivillosin K	O-Sen	2-MeBut

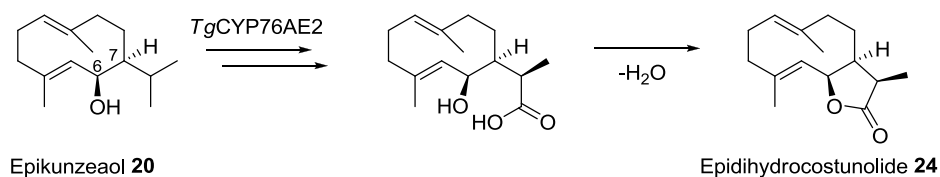
But = Butanoyl, Sen = Seneciyl, Ang = Angeloyl, Hex = Hexanoyl,
Hep = Heptanoyl, Oct = Octanoyl, *i*Val = Isovaleroyl.

Although the full biosynthetic pathway of thapsigargin and related compounds has not yet been established, several aspects of the early stages of biosynthesis have been elucidated. It has been shown that the rather unusual C-6 configuration is likely introduced at an early stage by the action of the sesquiterpene synthase *TgTPS2* found in the roots of *T. garganica*,²³ which converts FPP **11** into epikunzeaol **20** via the proposed mechanism in Scheme 5. A 1,3-hydride shift to allyl cation **21** allows for the installation of the C-6 hydroxyl without the need for a discrete oxidation step. This was evidenced by the detection of secondary metabolites **22** and **23**, which arise from carbocation **21** in the absence of a water quench.



Scheme 5. Early thapsigargin biosynthesis stages establishing C-6 configuration.

Later investigation also identified a sesquiterpene specific cytochrome P450, *TgCYP76AE2*, present in *T. garganica*, which completely converts epikunzeaol **20** into a possible downstream metabolite epidihydrocostunolide **24** (Scheme 6).²⁴



Scheme 6. *TgCYP76AE2* mediated oxidation of epikunzeaol.

²³ Pickel, B.; Drew, D. P.; Manczak, T.; Weitzel, C.; Simonsen, H. T.; Ro, D.-K. *Biochem. J.* **2012**, 448, 261.

²⁴ Anderson, T. B.; Martinez-Swatson, K. A.; Rasmussen, S. A.; Boughton, B. A.; Jørgenson, K.; Andersen-Ranberg, J.; Nyberg, N.; Christensen, S. B.; Simonsen, H. T. *Plant Physiol.* **2017**, 174, 56.

1.3 Thapsigargin biological activity

1.3.1 SERCA inhibition and mode of action

The sarco/endoplasmic reticulum Ca^{2+} ATPase is part of a family known as P-type ATPases. P-ATPases are known throughout nature as cross-membrane ion and lipid pumps, ²⁵ utilising ATP as an energy source. SERCA is encoded for by three major specific gene sequences in the human genome, each resulting in a SERCA paralog. These are expressed at different levels within different cell types, such as cardiac and skeletal muscles, and also non-muscle tissues such as lymphocytes, salivary gland and platelets, amongst others. ^{26, 27, 28}

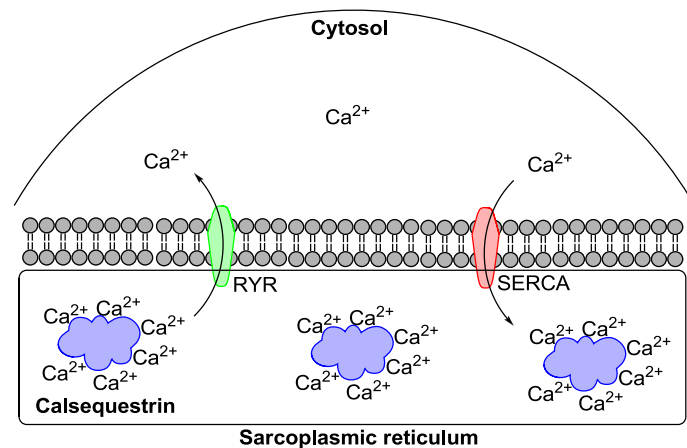


Figure 3. Calcium transport between the cytosol and SR.

SERCA is found in the membrane of the sarcoplasmic reticulum (SR), or the smooth endoplasmic reticulum, which acts as a storage for Ca^{2+} , to be released during cell stimulation. Ca^{2+} is released quickly by ryanodine receptors (RYR) into the cytoplasm, after which it diffuses and activates receptors according to the function of the cell. ²⁹ SERCA then gradually pumps the Ca^{2+} back into the lumen of the sarcoplasmic reticulum,

²⁵ Møller, J. V.; Juul, B.; Le Maire, M. *Biochim. Biophys. Acta* **1996**, 1286, 1.

²⁶ Guglielmi, V.; Vattemi, G.; Gualandi, F.; Voermans, N. C.; Marini, M.; Scotton, C.; Pegoraro, E.; Oosterhof, A.; Kósa, M.; Zádor, E.; Valente, E. M.; De Grandis, D.; Neri, M.; Codemo, V.; Novelli, A.; van Kuppevelt, T. H.; Dallapiccola, B.; van Engelen, B. G.; Ferlini, A.; Tomelleri, G. *Mol. Genet. Metab.* **2013**, 110, 162.

²⁷ Dode, L.; Wuytack, F.; Kools, P. F.; Baba-Aissa, F.; Raeymaekers, L.; Briké, F.; van de Ven, W. J.; Casteels, R.; Brik F. *Biochem. J.* **1996**, 318, 689.

²⁸ Liu, L. H.; Paul, R. J.; Sutliff, R. L.; Miller, M. L.; Lorenz, J. N.; Pun, R. Y. K.; Duffy, J. J.; Doetschman, T.; Kimura, Y.; MacLennan, D. H.; Hoying, J. B.; Shull, G.E. *J. Biol. Chem.* **1997**, 272, 30538.

²⁹ Schiemann, A. H.; Paul, N.; Parker, R.; Pollock, N.; Bulger, T. F.; Stowell, K. M. *Anesth. Analg.* **2014**, 118, 375.

returning the levels of Ca^{2+} in the rest of the cell back to normal levels (Figure 3). In addition, free Ca^{2+} can be bound to a protein called calsequestrin in the SR, which serves to lower the Ca^{2+} concentration gradient that SERCA has to work against.³⁰

Thapsigargin is a potent non-competitive, irreversible inhibitor of SERCA proteins, active at sub-nanomolar concentrations ($K_D = 0.4 \text{ nM}$), and has been a target of interest for its cytotoxic and calcium concentration modulation effects.^{31, 32} Crystal structures obtained in 2000 by Toyoshima *et al.* showed, in detail, some of the mechanisms in calcium transport and inhibition by thapsigargin.^{33, 34} The two crystal structures shown in Figure 4 are calcium-bound SERCA **E1**(Ca^{2+}) and thapsigargin-bound SERCA **E2**(Tg).

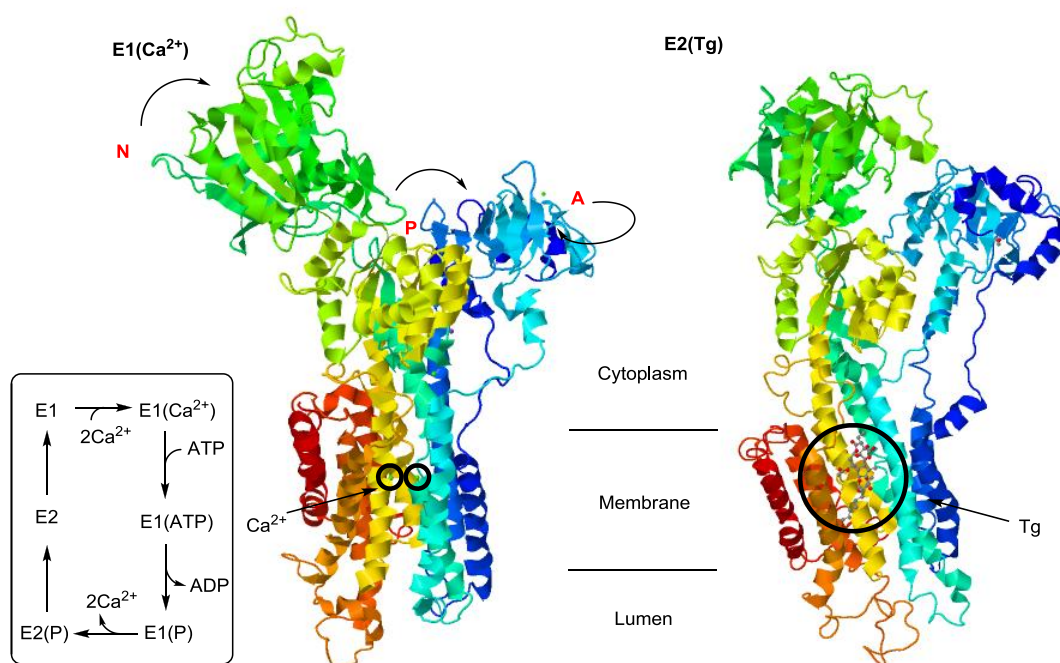


Figure 4. SERCA crystal structures showing binding to both Ca^{2+} and thapsigargin. The three cytoplasmic domains N, P and A movement between **E1**(Ca^{2+}) and **E2**(Tg) is shown by arrows.^{33,35,36}

E1(Ca^{2+}) illustrates the beginning of the calcium transport cycle, before phosphorylation. The two calcium ions highlighted are bound in an oxygen rich environment after being

³⁰ Slupsky, J. R.; Ohnishi, M.; Carpenter, M. R.; Reithmeier, R. A. F. *Biochemistry*, **1987**, 26, 6539.

³¹ Michelangeli, F.; East, J.M. *Biochem. Soc. Trans.* **2011**, 39, 789.

³² Treiman, C.; Caspersen, C.; Christensen, S. B. *Trends in Pharm. Sci.* **1998**, 19, 131.

³³ Toyoshima, C.; Nakasako, M.; Nomura, H.; Ogawa, H. *Nature* **2000**, 405, 647.

³⁴ Toyoshima, C.; Nomura, H. *Nature* **2002**, 418, 605.

³⁵ Takahashi, M.; Kondou, Y.; Toyoshima, C. *Proc. Natl. Acad. Sci. Usa*, **2007**, 104, 5800.

³⁶ Image generated using Jmol: an open-source Java viewer for chemical structures in 3D.
<http://www.jmol.org/>

guided into the pocket by a series of residues via hydrogen bonding. As the Ca^{2+} reaches the binding site, they induce a significant conformation change in **E1** not only in the transmembrane helices but also to the cytoplasmic domains. This change to **E1(Ca²⁺)** exposes Arg 351 in the P domain and allows a phosphorylation to take place on that residue. Phosphorylation causes a large-scale conformational change whereby domains N, P and A block off the ion channel on the cytoplasm side by forming a compact structure **E1(P)**. This is accompanied by a rearrangement of the transmembrane helices which encompass the Ca^{2+} ions. This exposes the Ca^{2+} to less favourable hydrophobic residues after which binding affinity is reduced by a factor of 3 and subsequently they are released into the SR lumen.³⁷ This calcium-released structure **E2** is analogous to **E2(Tg)**,³⁸ a crucial insight as it allows direct comparison of **E1(Ca²⁺)** and **E2(Tg)**. Irreversible SERCA inhibition also stems from the conformational similarity of **E2** and **E2(Tg)**, as **E2** retains the closed cytoplasmic head of **E1(P)** and requires a conformational change to **E1** before another pair of Ca^{2+} ions can be bound.

It is therefore interesting to note that when thapsigargin irreversibly binds to SERCA in **E2(Tg)**, it does so in a hydrophobic pocket that is only favourably configured in the **E2** state, but has been shown in the crystal structures to be too small for thapsigargin to enter in **E1(Ca²⁺)**. Tg binding thus restricts the helical movements, which accounts for the stability of **E2(Tg)** compared to solubilised SERCA, which denatures in the absence of phospholipid support as well as high concentrations of Ca^{2+} .³⁹ This restricted movement keeps the N, P and A domains locked in place and prevents any further Ca^{2+} transport. Many hydrophobic residues on three separate helices (M3, M5 and M7) are implicated in the binding affinity of thapsigargin to SERCA (Figure 5), however only one weak hydrogen bond between Ile 829 and the O-8 ester could be established.^{34,40}

³⁷ MacLennan, D. H.; Rice, W. J.; Green, N. W. *J. Biol. Chem.*, **1997**, 272, 28815.

³⁸ Sagara, Y.; Inesi, G. *J. Biol. Chem.* **1991**, 266, 13503.

³⁹ Pikula, S.; Mullner, N.; Dux, L.; Martonosi, A. *J. Biol. Chem.* **1988**, 263, 5277.

⁴⁰ Singh, P.; Mhaka, A. M.; Christensen, S. B.; Gray, J. J.; Denmeade, S. R.; Isaacs, J. *J. Med. Chem.* **2005**, 48, 3005.

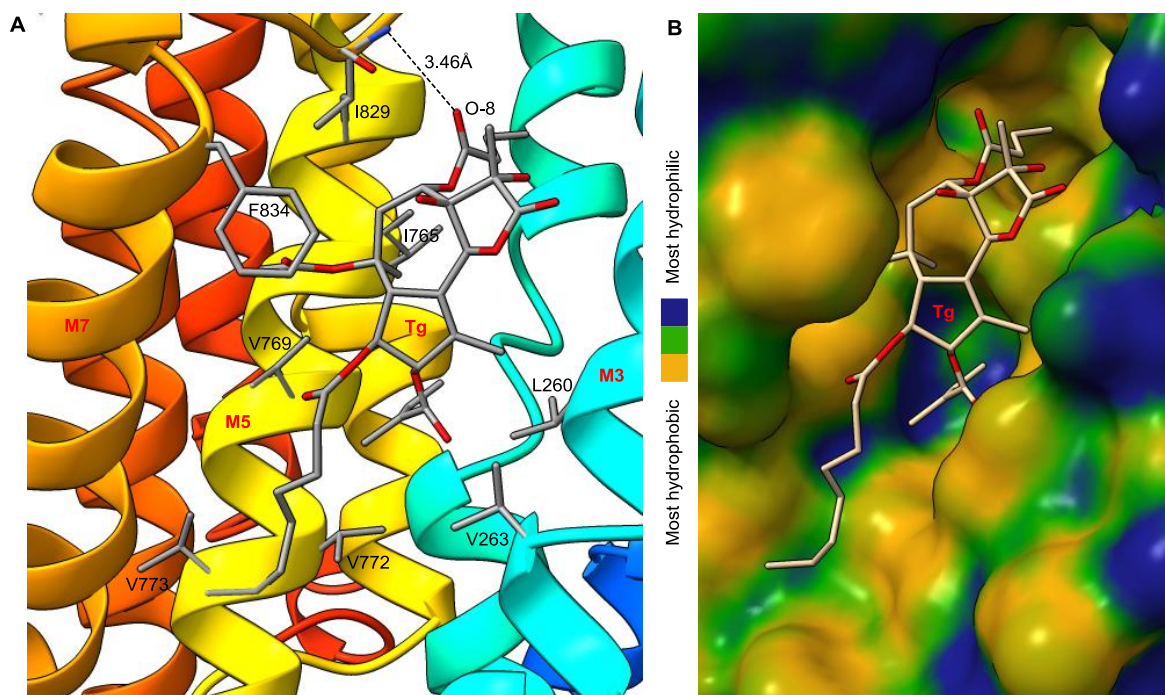


Figure 5. (A) Location of hydrophobic residues in the E2(Tg) binding pocket. (B) Calculated hydrophobic potential colour-mapped onto the SERCA(E2) Connolly surface.^{34,41,42,43}

1.3.2 Thapsigargin analogues

Before the crystal structure elucidation in 2000 by Toyoshima *et al.*, structure-activity relationship (SAR) studies yielded many semi-synthetic analogues produced from the selective modification of natural thapsigargin (Figure 6). Some of the most important insights from the SAR investigations concern the various oxygenated positions surrounding the thapsigargin core.

⁴¹ Molecular graphics and analyses performed with UCSF ChimeraX, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California.
<http://www.rbvi.ucsf.edu/chimerax/>

⁴² Goddard, T. D.; Huang, C. C.; Meng, E. C.; Pettersen, E. F.; Couch, G. S.; Morris, J. H.; Ferrin, T. E. *Protein Sci.* **2018**, 27, 14.

⁴³ Laguerre, M.; Saux, M.; Dubost, J. P.; Carpy, A. *Pharm. Pharmacol. Commun.* **1997**, 3, 217.

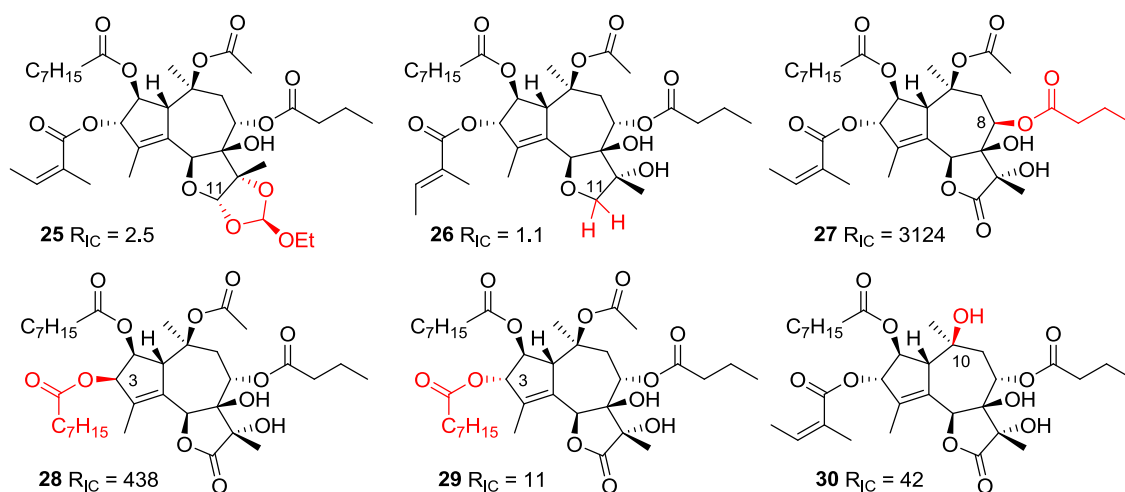


Figure 6. Semi-synthetic thapsigargin analogues. Relative activity (R_{IC}) is obtained by dividing the corresponding IC_{50} value by the IC_{50} value of thapsigargin **1**.

Unlike many guaianolides,⁴⁴ the biological activity of thapsigargin does not seem to critically depend on the γ -lactone as is demonstrated by the high relative activity of acetal **25** and tetrahydrofuran **26**. The inversion of the C-8 and C-3 stereocenters in **27** and **28** respectively is accompanied by a large drop in activity not accounted for by the replacement of the C-3 angeloyl by octanoyl alone as shown by natural epimer **29**. Similarly the lack of the C-10 acetate in analogue **30** demonstrates the moiety's involvement in the inhibitory potential of thapsigargin.^{45,46}

These results can be rationalised when compared with Tg-bound SERCA crystal structures. The binding site mapped out in figure 5 (B) clearly shows two hydrophobic pockets that fit the natural orientation of the C-8 and C-3 esters, while the lack of significant hydrogen bonding around the lactone region allows substantial modification without impacting activity. When combined, these results can be used for the rational design of potent SERCA inhibitors; although the C-10 acetate of **1** contributes a significant hydrophobic interaction, the carbonyl moiety is also responsible for an unfavourable electrostatic interaction with Phe834 (Figure 7). This configuration is adopted as a consequence of

⁴⁴ Merfort, I. *Curr. Drug Targets* **2011**, 12, 1560.

⁴⁵ a) Christensen, S. B.; Hergenbahn, M.; Roeser, H.; Hecker, E. *J. Cancer Res. Clin. Oncol.* **1992**, 118, 344. b) Christensen, S. B.; Andersen, A.; Poulsen, J. C. J.; Treiman, M. *Febs Lett.* **1993**, 335, 345. c) Andersen, A.; Cornett, C.; Lauridsen, A.; Olsen, C. E.; Christensen, S. B. *Acta Chem. Scand.* **1994**, 48, 340 d) Nielsen, S. F.; Thastrup, O.; Pedersen, R.; Olsen, C. E.; Christensen, S. B. *J. Med. Chem.* **1995**, 38, 272 e) Christensen, S. B.; Andersen, A.; Smitt, U. W. *Prog. Chem. Org. Nat. Prod.* **1997**, 71, 129.

⁴⁶ Christensen, S. B.; Skytte, D. M.; Denmeade, S. R.; Dionne, C.; Møller, J. V.; Nissen, P.; Isaacs, J. T. *Anticancer Agents Med. Chem.* **2009**, 9, 276.

carbonyl dipole-dipole minimisations (with O-2, O-3 and O-10) and the conformational rigidity introduced by the C-4/5 olefin. Since nortrilobolide **19** possesses nearly the same inhibitory activity as thapsigargin,⁴⁷ C-2 deoxygenation would be expected to have a marginal impact on activity. Fully saturated analogue **31** then not only removes the unfavourable electrostatic interaction, but introduces a new favourable electrostatic attraction between the partial positive charge of the acetate carbonyl carbon and the electron-rich Phe834 π -system. Indeed, this rational design of **31** leads to a 10-fold increase in inhibitory potential compared to thapsigargin.⁴⁸

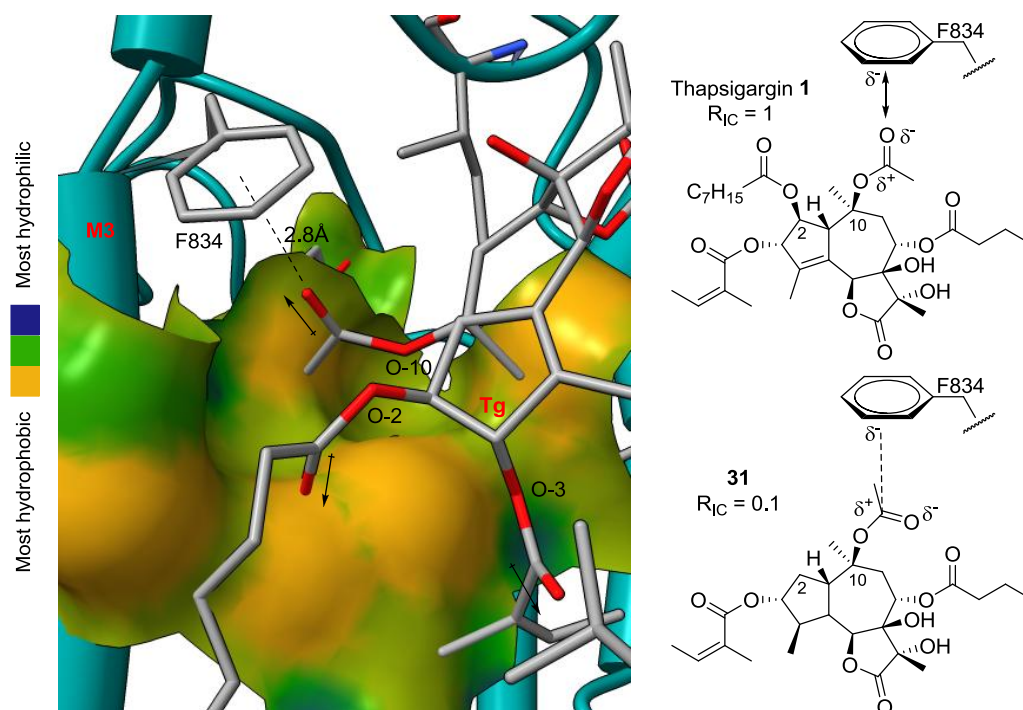


Figure 7. Orientation of the Tg and **x29** C-10 acetate relative to Phe834 alongside a partial hydrophobic potential surface map.

It is important to note that although many peripheral modifications of Tg exist, to date there have been no reports of [5,7] core modified analogues, leaving unexplored chemical space that is yet to be investigated.

⁴⁷ Søhoel, H.; Jensen, A. M. L.; Møller, J. V.; Nissen, P.; Denmeade, S. R.; Isaacs, J. T.; Olsen, C. E.; Christensen, S. B. *Bioorganic Med. Chem.* **2006**, *14*, 2810.

⁴⁸ Søhoel, H.; Liljefors, T.; Ley, S. V.; Olivier, S. F.; Antonello, A.; Smith, M. D.; Olsen, C. E.; Isaacs, J. T.; Christensen, S. B. *J. Med. Chem.* **2005**, *48*, 7005.

1.3.3 Prostate cancer

Prostate cancer is the fifth leading cause of cancer-related deaths in men world-wide.⁴⁹ Prostate cancer occurs almost exclusively in men over the age of 50 and is usually slow growing, with the prognosis being a long or complete life when detected locally and early, but it also poses a problem for the effective treatment of metastatic prostate cancer. The basis of chemotherapy is centred on the use of drugs to systemically target cell mitosis, disproportionately affecting the fast division of malignant tumour cells, and it is thus ineffective against the slow proliferation of prostate cancer. Standard frontline treatment of metastatic prostate cancer includes the use of hormone therapy as a subpopulation of prostate cancer tumours are androgen-dependent and will undergo apoptosis in response to reduced levels of testosterone. However, the remaining tumour cells are androgen-independent (castration-resistant) and growth relapse occurs once the tumour becomes unresponsive to hormone suppression.⁵⁰ Many second-line chemotherapeutic options exist, the vast majority acting by the classical approach of inhibiting the mitotic phase of the cancer cells, thereby increasing life-expectancy significantly. However, due to the relatively low activity of antimitotic drugs in this setting, once a castration-resistant metastatic stage is reached it is considered eventually fatal.⁵¹

Thapsigargin's mode of action is different from standard chemical treatment options and is effective against both normal and castration-resistant metastatic prostate cancer cells. The indiscriminate high cytotoxicity exhibited by Tg is also the drawback to this approach, as systemic use analogous to standard antimitotic therapies would result in benign cells being attacked with equal potency.⁵²

Two peptidases have recently become the focus of targeted therapeutics in relation to prostate cancer. Prostate specific antigen (PSA) is produced by prostate cells where it serves multiple functions, from liquefying semen to dissolving the cervical mucus after ejaculation, allowing free movement for the sperm cells.⁵³ Because PSA is produced by

⁴⁹ "World Cancer Report 2014", **2014**, World Health Organisation.

⁵⁰ Seruga, B.; Ocana, A.; Tannock, I. F. *Nat. Rev. Clin. Oncol.*, **2011**, 8, 12.

⁵¹ Bandini, M.; Pompe, R. S.; Marchioni, M.; Zaffuto, E.; Gandaglia, G.; Fossati, N.; Cindolo, L.; Montorsi, F.; Briganti, A.; Saad, F.; et al. *Int. Urol. Nephrol.* **2018**, 50, 71.

⁵² Denmeade, S. R.; Jakobsen, C. M.; Janssen, S.; Khan, S. R.; Garrett, E. S.; Lilja, H.; Christensen, S. B.; Isaacs, J. T. *J. Nat. Cancer. Inst.*, **2003**, 95, 990.

⁵³ Balk, S. P.; Ko, Y. J.; Bubley, G. J. *J. Clin. Oncol.*, **2003**, 21, 383.

prostate epithelial cells and found almost exclusively in benign as well as malignant prostate tissue, it has great potential as a tool to target drugs directly at metastatic prostate cancer tumours.⁵⁴ Prostate specific membrane antigen (PSMA) is normally produced in healthy epithelial prostate cells, as well as parts of the liver, kidneys, the small intestine and in the central nervous system.⁵⁵ PSMA expression is upregulated in prostate cancer cells, and subsequently they contain over 1000 times the concentration of PSMA compared to PSMA-containing non-prostate tissue.⁵⁶ Importantly, however, PSMA is found at significant levels in the endothelium of the neovasculature supporting all solid tumour types; no PSMA expression is found in comparable benign vasculature.⁵⁷

Prodrug **32** (G115) was developed to be cleaved exclusively by PSA (Figure 8).^{46,52,58} Analogue **L12ADT** has a slightly lower inhibitory potential (IC₅₀) compared with thapsigargin, but a nearly identical cytotoxic potential (LC₅₀) towards prostate cancer cell lines. A long linker (more than 8 methylene units) was necessary as the attachment of a short linker causes the amino group necessary for peptide coupling to occupy the hydrophobic pocket reserved for the O-8 acyl group (Figure 4), causing unfavourable interactions. Additionally, a leucine had to be incorporated into the active analogue structure, as PSA studies indicated the need for amino acids to be present on both sides of the cleavage site.⁵⁹ The attached Mu-His-Ser-Ser-Lys-Leu-Gln peptide sequence is recognised exclusively by PSA and cleaved at the indicated Leu-Gln site, ensuring **L12ADT** is delivered exclusively to localised areas. This is exemplified by *in vivo* stability in mice, with less than 0.5% of **32** hydrolysed after 24h.⁵²

⁵⁴ Velonas, V. M.; Woo, H. H.; dos Remedios, C. G.; Assinder, S. J. *Int. J. Mol. Sci.* **2013**, *14*, 11034.

⁵⁵ Barinka, C.; Sáša, P.; Sklenár, J.; Man, P.; Bezouska, K.; Slusher, B. S.; Konvalinka, J.; *Protein Sci.*, **2004**, *13*, 1627.

⁵⁶ Murphy, G. P.; Su, S.; Jarisch, J.; Kenny, G. M. *Prostate* **2000**, *42*, 318.

⁵⁷ Chang, S. S.; O'Keefe, D. S.; Bacich, D. J.; Reuter, V. E.; Heston, W. D. W.; Gaudin, P. B. *Clin. Cancer Res.* **1999**, *5*, 2674.

⁵⁸ Denmeade, S. R.; Isaacs, J. T. *Cancer Biol. Ther.* **2005**, *4*, 14.

⁵⁹ Denmeade, S. R.; Nagy, A.; Gao, J.; Lilja, H.; Schally, A. V.; Isaacs, J. T. *Cancer Res.* **1998**, *58*, 2537.

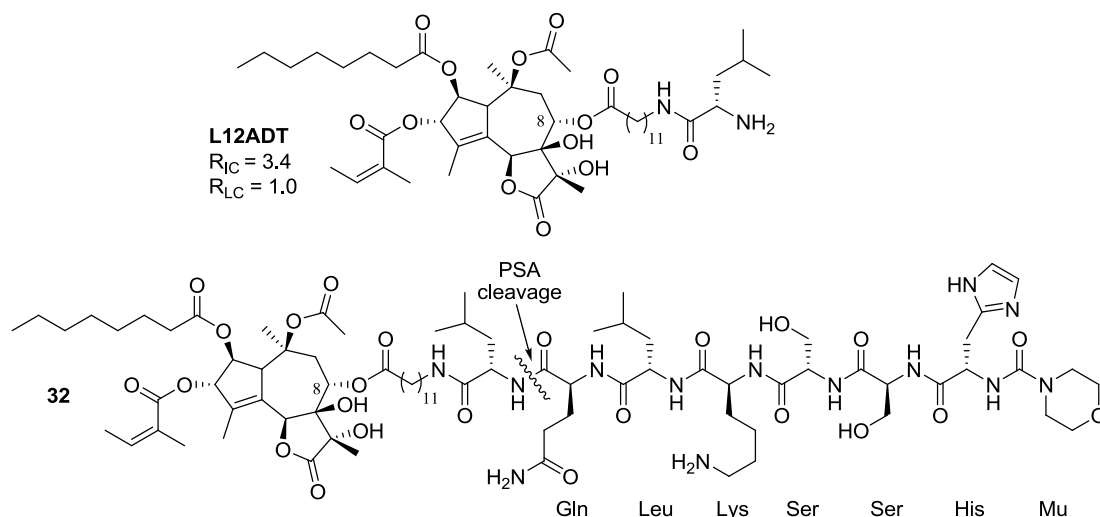


Figure 8. PSA specific activation of prodrug G115.

Another prodrug candidate **33**, (G202, mipsagargin), uses PSMA to effect cleavage of its peptide side chain (Figure 9).^{60, 61} Although PSMA is also expressed in some benign cells, expression typically occurs beyond the epithelial layers where G202 does not penetrate. In addition, the blood-brain barrier is thought to prevent significant amounts of the highly polar prodrug accumulating in the central nervous system.⁶²

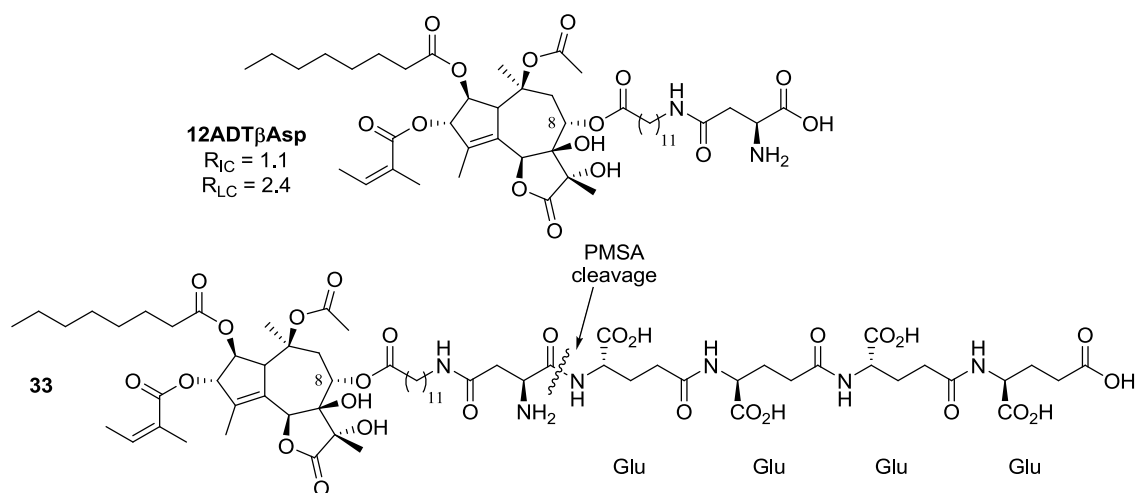


Figure 9. G202/Mipsagargin.

⁶⁰ Denmeade, S. R.; Mhaka, A. M.; Rosen, D. M.; Brennen, W. N.; Dalrymple, S.; Dach, I.; Olesen, C.; Gurel, B.; Demarzo, A. M. Wilding, G.; Carducci, M. A.; Dionne, C. A.; Møller, J. V.; Nissen, P.; Christensen, S. B.; Isaacs, J. T. *Sci. Transl. Med.*, **2012**, *4*, 140ra86.

⁶¹ Doan, N. T. Q.; Paulsen, E. S.; Sehgal, P.; Møller, J. V.; Nissen, P.; Denmeade, S. R.; Isaacs, J. T.; Dionne, C. A.; Christensen, S. B. *Steroids*, **2015**, *97*, 2.

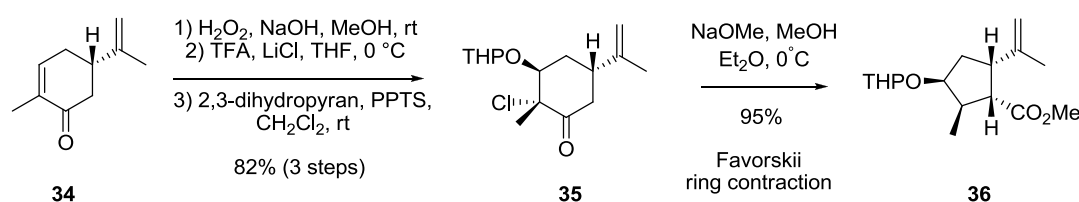
⁶² Milowsky, M. I.; Nanus, D. M.; Kostakoglu, L.; Sheehan, C. E.; Vallabhajosula, S.; Goldsmith, S. J.; Ross, J. S.; Bander, N. H. *J. Clin. Oncol.* **2007**, *25*, 540.

Prodrug **33** proved to be stable in human plasma and to a range of purified human peptidases other than PSMA. This was again demonstrated in mice where molar equivalent dosing of **33** >150× the LD₁₀₀ of Tg produced no significant systemic toxicity. A further advantage to targeting vascular epithelial cells is that **12ADTβAsp** is released extracellularly, additionally affecting those cells which do not express PSMA in the tumour environment. Mipsagargin has undergone a phase II clinical trial in patients with Nexavar-refractory hepatocellular carcinoma and has been granted Orphan Drug designation by the U.S. Food and Drug Administration. Provided clinical trials prove successful, annual demand for Tg **1** is expected to be in the order of 1 ton per annum.⁶³ Since Tg is currently only available in large quantities from wild *T. Garganica*, a successful synthetic route is preferred.

1.4 Previous synthetic efforts towards thapsigargin

1.4.1 Ley's synthesis of thapsigargin

Three total syntheses of thapsigargin have been published to date. The Ley total synthesis, completed in 2007, starts from (*S*)-carvone **34** in a linear sequence of 42 steps with an overall yield of 0.62%.⁶⁴ The synthesis starts with a Favorskii ring contraction of α-chloroketone **35** to give methyl ester **36** as a single diastereomer on >100 g scale (Scheme 7).



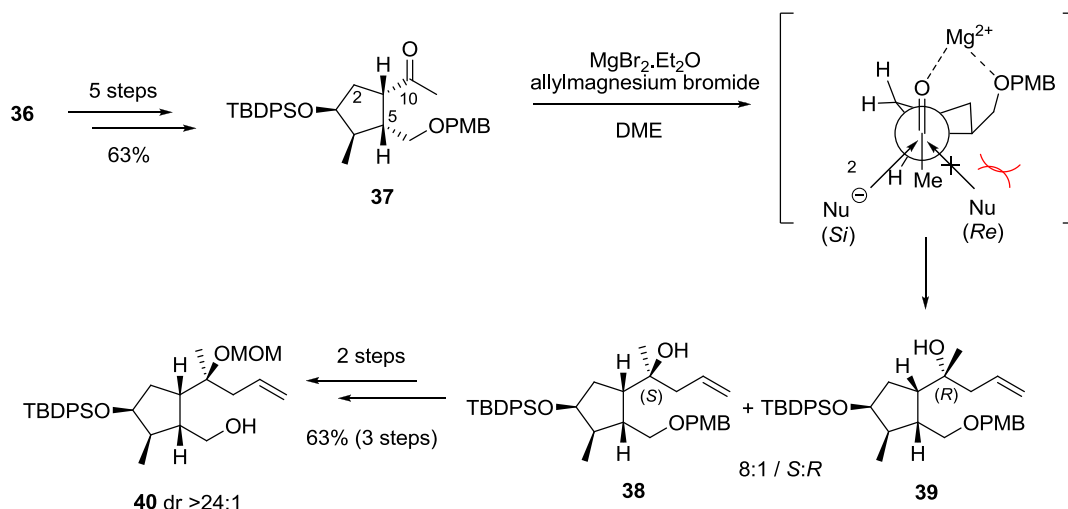
Scheme 7. Favorskii ring contraction.

Felkin-Anh chelation-assisted addition of allylmagnesium bromide onto C-10 ketone **37** yields a consistent diastereomeric ratio of 8:1 in favour of the desired diastereomer **38**

⁶³ Quynh Doan, N.; Christensen, S. *Curr. Pharm. Des.* **2015**, *21*, 5501.

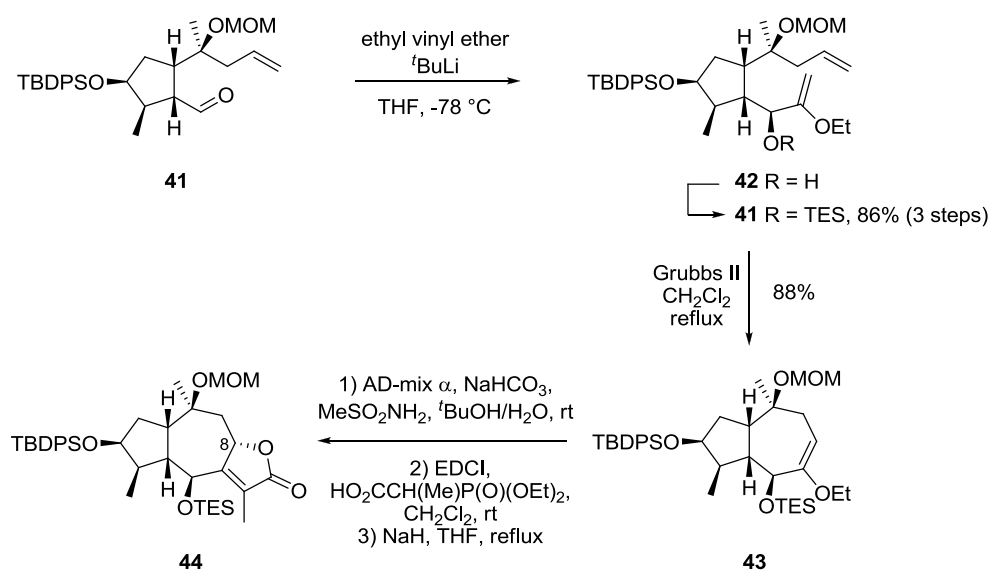
⁶⁴ a) Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Olivier, S.; Högenauer, K.; Simic, O.; Antonello, A.; Hüniger, U.; Smith, M. D.; Ley, S. V. *Chem. Eur. J.*, **2007**, *13*, 5688. b) Ball, M.; Andrews, S. P.; Wierschem, F.; Cleator, E.; Smith, M. D.; Ley, S. V. *Org. Lett.*, **2007**, *9*, 663

(Scheme 8). The undesired diastereomer **39** can be removed via column chromatography after derivation to **40**.



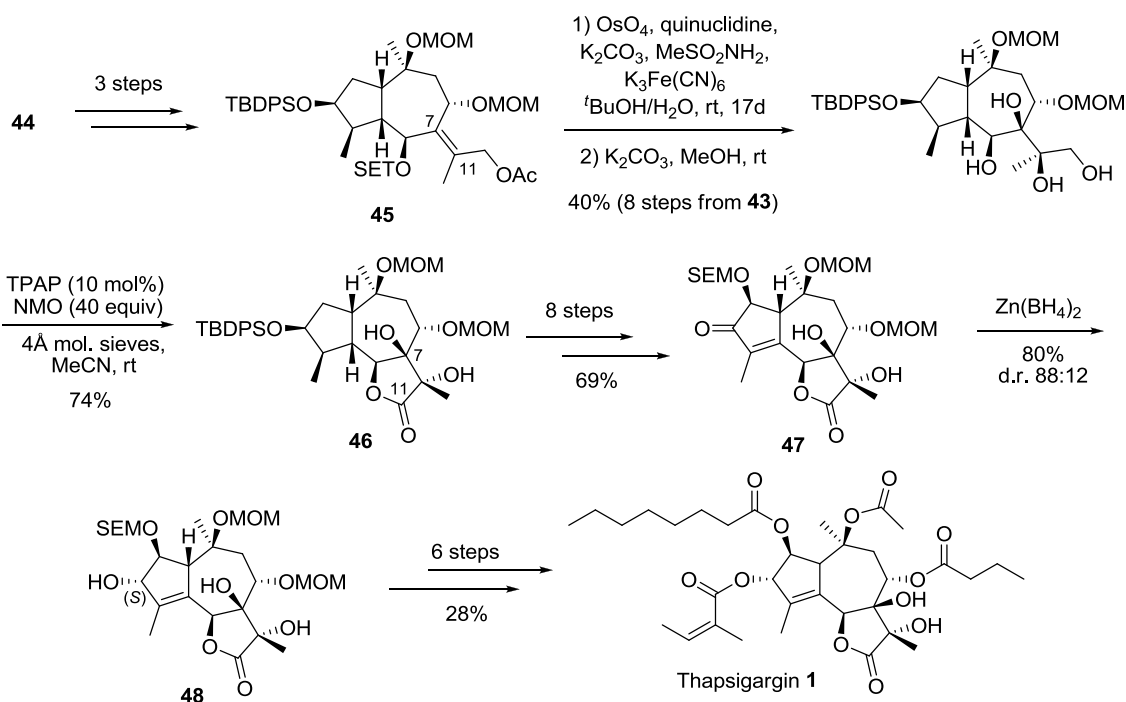
Scheme 8. Felkin-Anh controlled allylation.

Addition of lithiated ethyl vinyl ether under Felkin-Anh control to aldehyde **41** afforded **42** as an exclusive diastereomer, followed by ring-closing metathesis of protected alcohol **42** to give key bicycle **43** in good yield. A further three steps were required to complete the carbon skeleton (Scheme 9): hydroxylation of the key C-8 position diastereoselectively under Sharpless conditions and generation of lactone **44** via a tethered Horner-Wadsworth-Emmons reaction.



Scheme 9. Felkin-Anh addition and ring-closing metathesis.

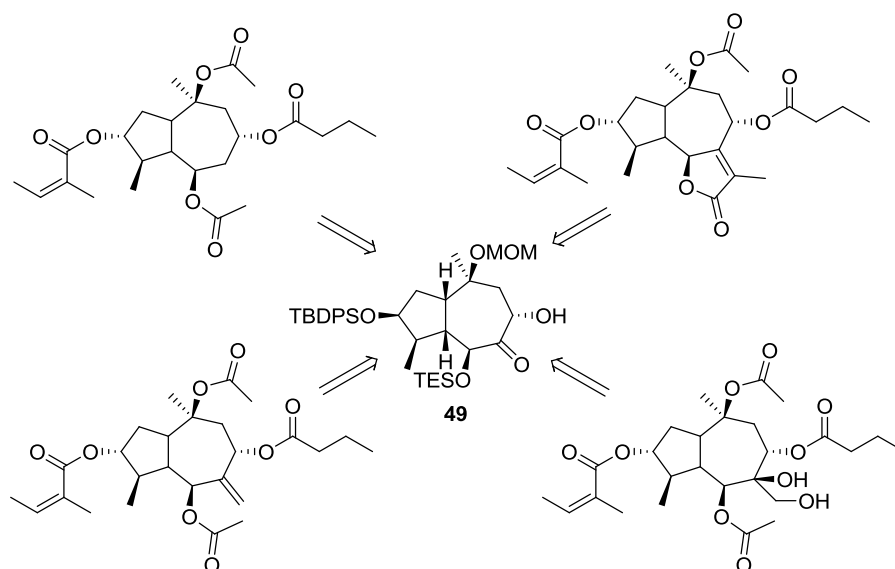
Dihydroxylation of **45** oxygenates the crucial C-7/C-11 positions with the correct configuration for the final lactone **46**. Late-stage substrate-controlled reduction of enone **47** affords the desired *S* configuration at C-3. Peripheral modification of **48** completes the total synthesis of thapsigargin in 6 steps (Scheme 10).



Scheme 10. Dihydroxylation, late stage reduction and endgame.

The strength of this synthesis lies in the ability to branch off at different stages of the synthesis to produce both natural and unnatural analogues. Not only was the total synthesis of thapsigargin completed, but thapsivillosin C and F, trilobolide and nortrilobolide were also synthesised, and later routes were devised to unnatural analogues from a single precursor present in the total synthesis, **49** (Scheme 11).⁶⁵ However, the number of steps involved make it prohibitive for large scale industrial applications. Additionally, there has been no exploration of modifications involving the [5,7] guaianolide core, but this is not an inherent problem with the synthesis as the Felkin-Ahn allylation of **37** can be modified to provide other skeletal analogues.

⁶⁵ Andrews, S. P.; Tait, M. M.; Ball, M.; Ley, S. V. *Org. Biomol. Chem.* **2007**, 5, 1427.



Scheme 11. Unnatural analogue synthesis from a common precursor.

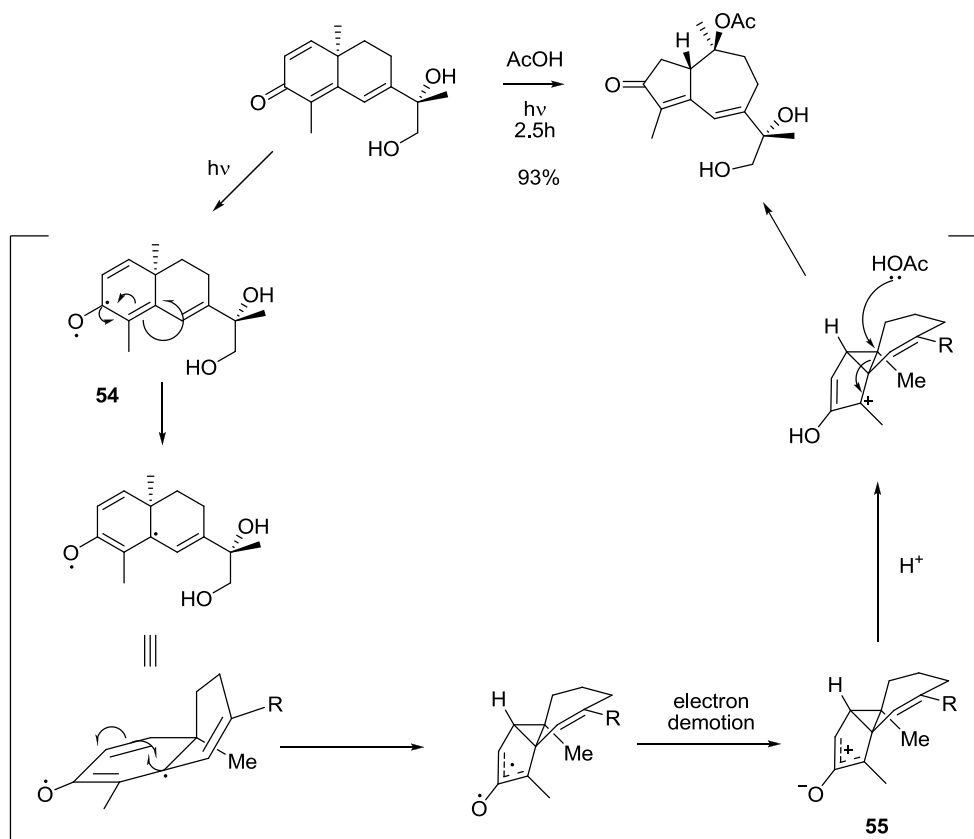
1.4.2 Baran's synthesis of thapsigargin

The Baran synthesis of thapsigargin was completed in 2017, in only 11 steps in length and has an overall yield of 0.33%.⁶⁶ Starting with a Robinson annulation between (+)-dihydrocarvone and ethyl vinyl ketone, all 15 skeletal carbons were installed immediately (Scheme 12). Bubbling molecular oxygen through the reaction mixture after the annulation event oxidised the C-6 position in one pot to deliver decalin **50** with complete stereoselectivity. Next, a one-pot, four-step procedure first generates the α -bromoketone from a pre-formed silyl enol ether, which is subjected to elimination conditions followed by silyl deprotection to generate an intermediate dienone. This dienone is then immediately converted *via* dehydration to the extended dienone using Burgess' reagent. Finally, dihydroxylation on the most electron-rich alkene provides diol **51** with moderate diastereoselectivity.

⁶⁶ Chu, H.; Smith, J. M.; Felding, J.; Baran, P. S. *ACS Cent. Sci.* **2017**, *3*, 47.

Key intermediate **52** for the planned photochemical rearrangement was obtained through a Riley oxidation after primary alcohol protection, followed by a Mitsunobu inversion of the obtained unnatural C-8 alcohol epimer to install the requisite butanoate moiety. Baran *et al.* then built on Massanet's photosynthetic approach to the [5,7] skeleton (Scheme 13),^{67,68} allowing dienone **52** to undergo a photochemical rearrangement to guaianolide skeleton **53**, with further oxidation and peripheral modifications completing the total synthesis. The dienone rearrangement is thought to involve the skeletal rearrangement of a diradical excited state **54**, subsequent electron demotion to the ground state zwitterion **55** and finally nucleophilic attack by acetic acid.

⁶⁸ Zimmerman, H. E.; Schuster, D. I. *J. Am. Chem. Soc.* **1962**, *84*, 4527.



Scheme 13. Massanet's approach to the guaianolide core.

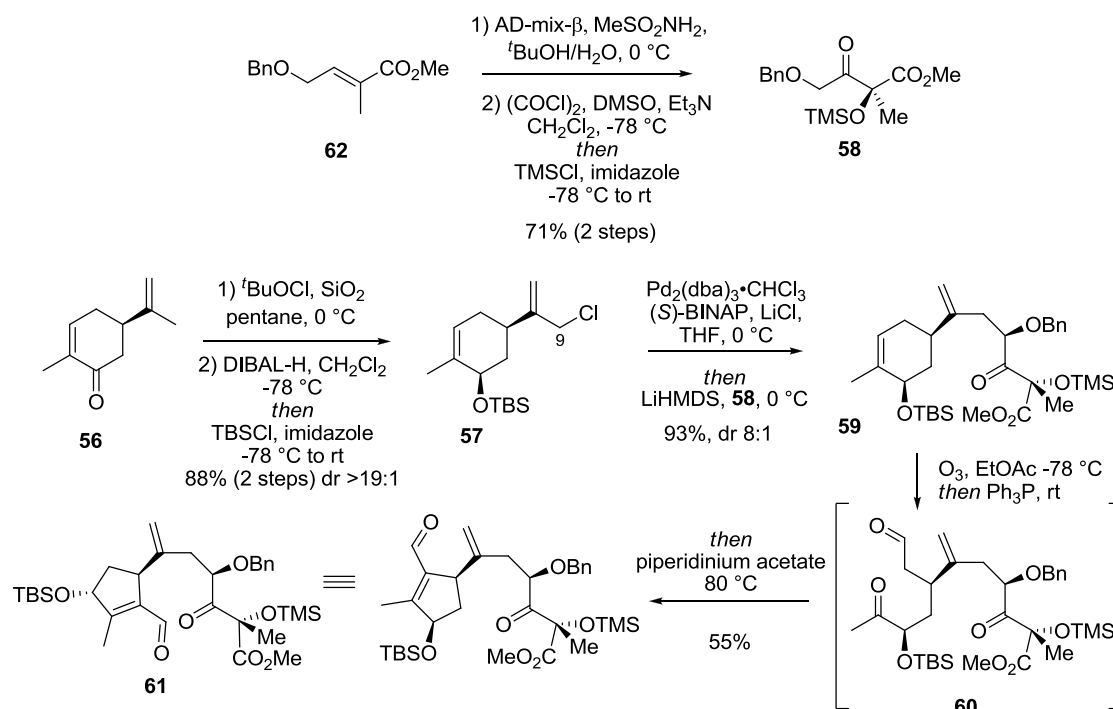
The strength of Baran's synthesis lies in its brevity and scalability. Reliance on well-known classical reactions (Sharpless dihydroxylation being the newest method in the synthesis) and avoidance of extreme temperature ranges makes it an attractive process in an industrial setting despite the rather low overall yield. Unfortunately the central photochemical rearrangement leaves little scope for skeletal modifications.

1.4.3 Evans' synthesis of thapsigargin

The group of P.A. Evans completed the second total synthesis of 2017; a short convergent synthesis consisting of 12 steps as the longest linear sequence and an overall yield of 5.8% from (*R*)-carvone **56**.⁶⁹ Starting with a selective allylic chlorination of **56**, followed by reduction and protection to construct allylation partner **57**, a diastereoselective Tsuji-Trost allylic alkylation with the enolate of fragment **58** as the nucleophile then installs all the required core carbons (Scheme 14). Ozonolysis of diene **59** affords the cleavage of the

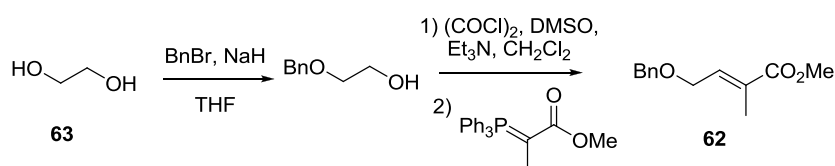
⁶⁹ Chen, D.; Evans, P. A. *J. Am. Chem. Soc.* **2017**, *139*, 6046.

electron-rich trisubstituted olefin as the major product. *In situ* aldol condensation of **60** neatly affords the challenging tetrasubstituted olefin as well the exocyclic aldehyde **61**.



Scheme 14. Evans' synthesis of fragment **61** from (*R*)-carvone.

Although not mentioned in the paper, starting material **62** is not readily commercially available and can be constructed in a classic 4-step sequence from ethylene glycol **63** (Scheme 15).⁷⁰

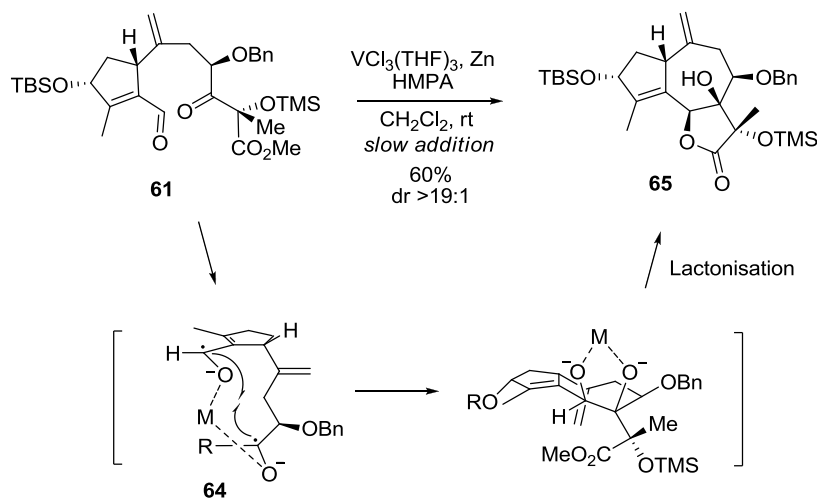


Scheme 15. Synthesis of starting material **62**.

The next stage involved the pinacol coupling of dicarbonyl **61** mediated by the *in situ* generation of the reagent $[\text{V}_2\text{Cl}_3(\text{THF})_6]_2[\text{Zn}_2\text{Cl}_6]$ (Scheme 16). Single electron reduction of both carbonyl groups generates the intermediate diradical dianion **64** which undergoes intramolecular coupling and lactonisation to the guainolide skeleton **65**. Coordination of both anions to the reducing agent ensures the near complete diastereoselective outcome of

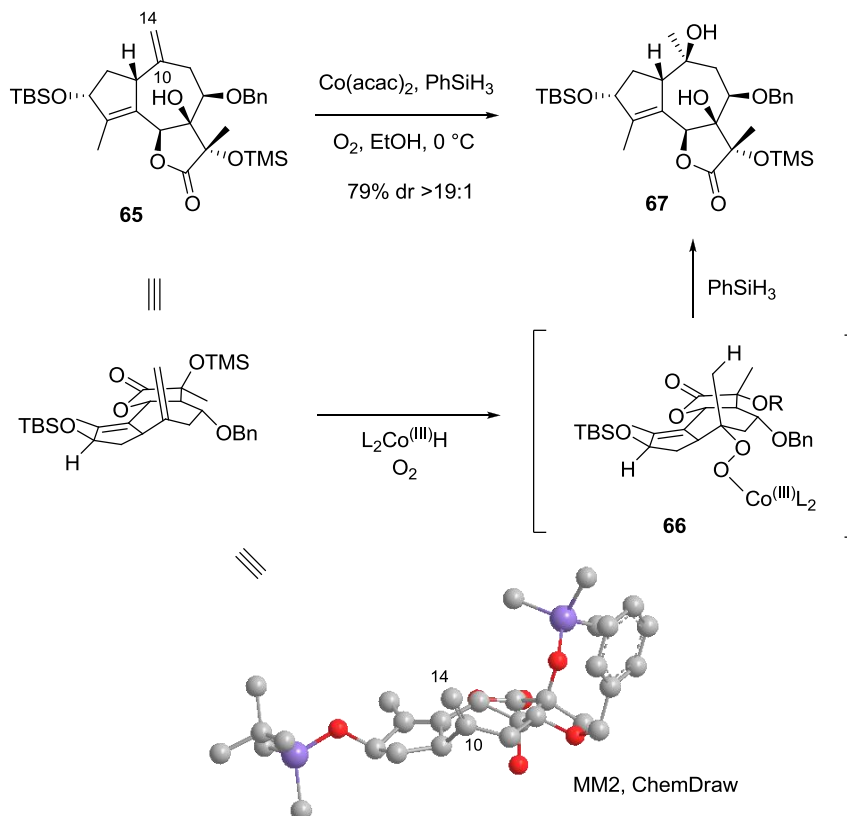
⁷⁰ Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *J. Am. Chem. Soc.* **1988**, 110, 10.

this reaction. Slow addition over the course of several hours was needed to ensure the minimisation of side reactions as a consequence of homocoupling.



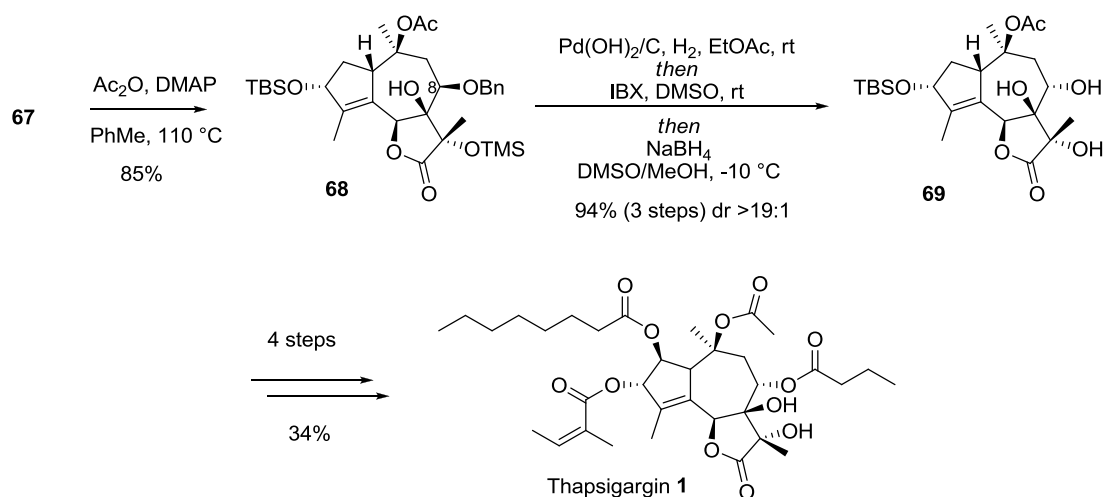
Scheme 16. Pinacol coupling and lactonisation.

The conformation of the [5,7,5] ring system in **65** then provides access for selective hydration across the C-10/C-14 olefin under Mukaiyama conditions to the correct face of the molecule as in **66** to give **67** (Scheme 17).



Scheme 17. Mukaiyama hydration.

Finally, the correct configuration of C-8 is set by substrate-controlled diastereoselective reduction in a sequential hydrogenation-oxidation-reduction procedure from benzyl ether **68** to triol **69**. Peripheral modifications similar to previous syntheses completes the total synthesis of thapsigargin (**1**) (Scheme 18).



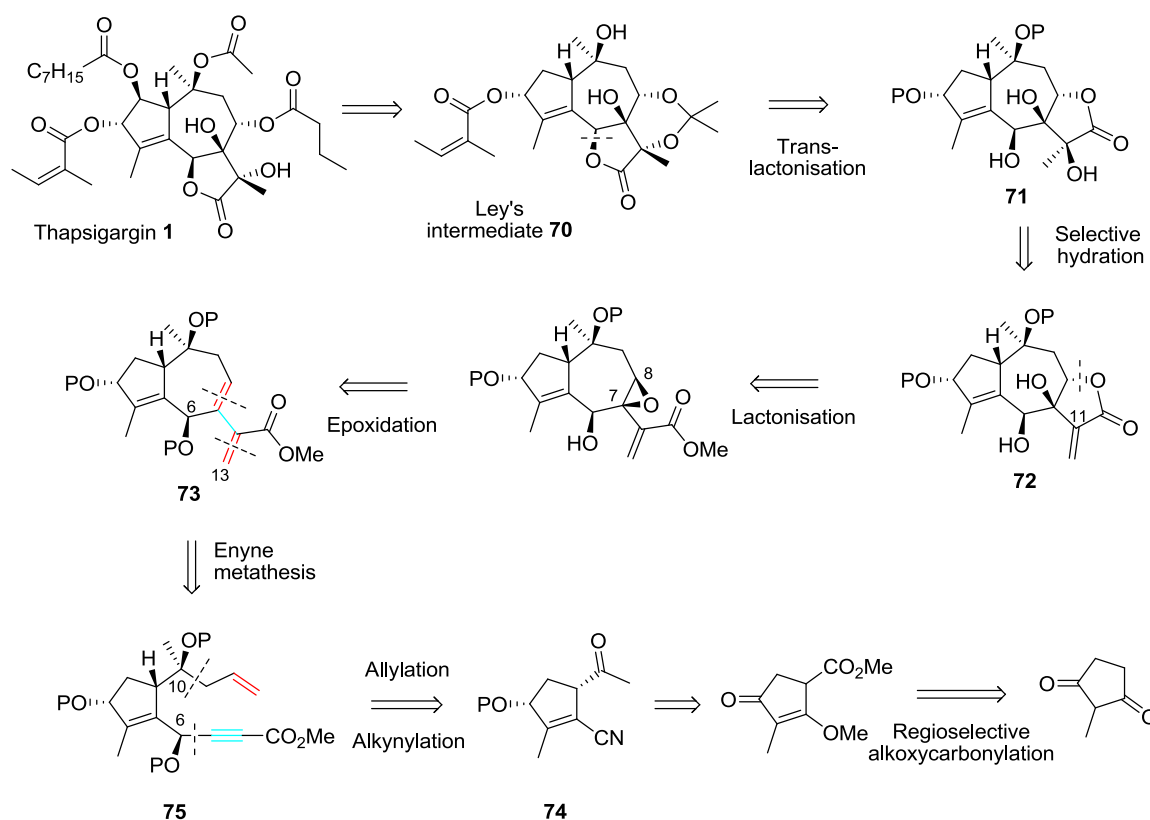
Scheme 18. Evans' thapsigargin endgame.

A similar drawback of this synthesis like many other total syntheses is the use of temperature extremes and thus a lack of large scalability. It is however a robust synthesis, relying on many established procedures for an efficient construction of the guaianolide core. It is also high-yielding and can easily provide many peripheral analogues on a research scale; however, the positioning of the C-9 chloride on **57** for the Tsuji-Trost allylic alkylation and the ketone on fragment **58** for the pinacol coupling exclude obvious modifications to the synthesis for the construction of skeletal analogues.

1.5 Project aims

As has been noted previously, total synthesis approaches to date have been varied but none have demonstrated sufficient flexibility to allow access to unnatural core-modified analogues of thapsigargin **1**. The only obvious candidate for this modification would be the Ley synthesis, but the length of this synthesis is prohibitive. Therefore a *flexible and rapid* approach to the guaianolide skeleton is required. To address this issue, a joint project was devised between the Prunet and F  r  zou groups. First it was envisioned that the retrosynthetic analysis of thapsigargin **1** leads to a formal synthesis *via* Ley's intermediate **70** in the synthesis of trilobolides, as the thapsigargin semi-synthesis by Christensen from

nortrilobolide **19** makes this a formal synthesis of thapsigargin (Scheme 19).⁷¹ Disconnection of the natural lactone carbon-oxygen bond to access lactone **71** was envisioned to provide the correct face of exocyclic methylene **72** for a hydration event to construct the challenging C-11 tetrasubstituted centre. Oxidation of the C-7/C-8 olefin could potentially be directed by the correctly configured C-6 hydroxyl group and would provide a means to the other contiguous tertiary alcohol on C-7, as well as providing a means to control the biologically crucial stereochemistry of C-8. The key step would then build on expertise within the Prunet group of utilising metathesis in natural product synthesis, using a ring-closing ene-yne metathesis (RCEYM) to construct the C-13 methylene unit **73**.

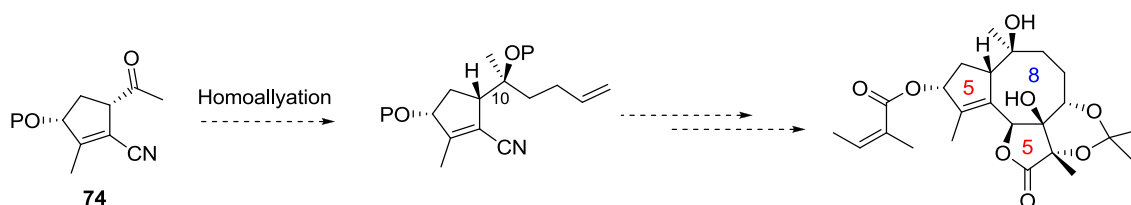


Scheme 19. A retrosynthetic approach to thapsigargin.

The first project aim would be the development of a successful, robust and enantioselective route to allylation precursors such as **74**. The second phase of the synthesis would include the construction of RCEYM precursors **75**. The final stage would then focus on the synthesis of the [5,7] bicycles and further elaboration to thapsigargin and analogues. The

⁷¹ Crestey, F.; Toma, M.; Christensen, S. B. *Tetrahedron Lett.* **2015**, 56, 5896.

second aim was to establish the proof of concept and deliver core-modified analogues of thapsigargin by our key RCEYM step. This analogue synthesis would then build on the work of Ley, chain length can be varied on demand. For instance, the addition of a homoallylic nucleophile can eventually lead to a [5,8,5]-core homologue of thapsigargin (Scheme 20).

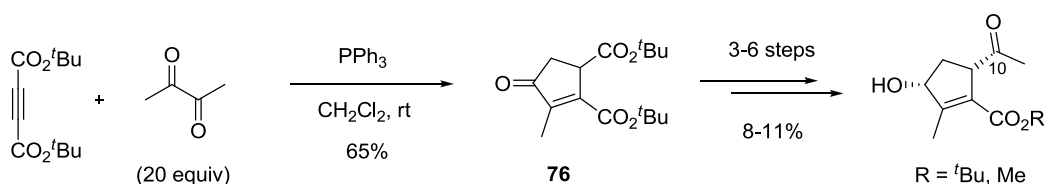


Scheme 20. Strategy towards the synthesis of core-modified analogues.

Chapter 2: Cyclopentenone derivatives

2.1 Previous work by Férézou *et al.*

Earlier work for this project conducted in the Férézou group by M. Jouanneau followed the broad retrosynthetic approach towards a fragment **75**.⁷² The first approach involved the use of a one-pot Michael-intramolecular Wittig reaction to synthesise cyclopentenone core **76** (Scheme 21).⁷³



Scheme 21. Sequential Michael-Wittig approach to cyclopentenones.

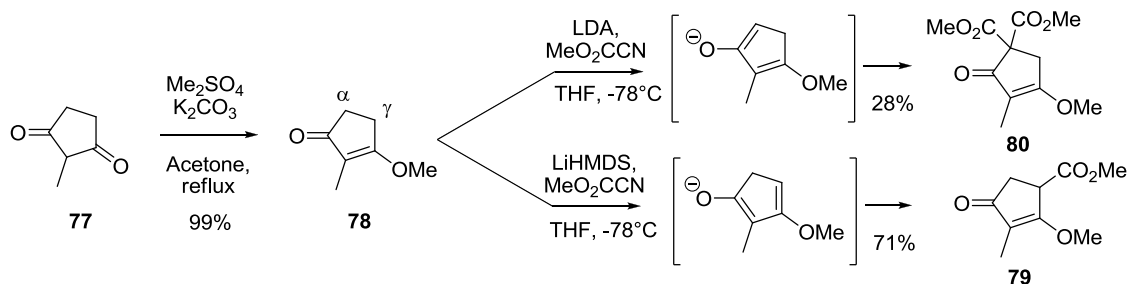
Subsequent derivatisation to the crucial C-10 ketone proved to be too low yielding to continue this synthetic strategy, therefore a new route was needed. Starting from commercial diketone **77**, deprotonation and methylation led to methyl enol ether **78**. According to a similar procedure from Ciufolini,⁷⁴ the generation of the thermodynamic enolate using LiHMDS (pKaH ~26) could be achieved at low temperature due to the weaker base favouring the thermodynamic enolate. Further assistance of the methyl enol ether by coordinating the lithium counterion promotes γ -deprotonation, much like α -deprotonation reactions are assisted by the adjacent carbonyl in the classic enolate formation (Scheme 22). The use of Mander's reagent⁷⁵ (methyl cyanofornate) then resulted in exclusive C-methoxycarbonylation to give ester **79**. The use of LDA (pKaH ~36) as a base however forms the kinetic enolate as evidenced by the generation of diester **80** as the major product.

⁷² Jouanneau, M. "Nouvelle approche vers la synthèse de la thapsigargine (guaianolides) par réaction de métathèse ényne cyclisante", thesis, Université Paris-Sud, **2014**.

⁷³ Jouanneau, M.; Tap, A.; Ardisson, J.; Férézou, J.-P. *Synlett* **2014**, 25, 2171.

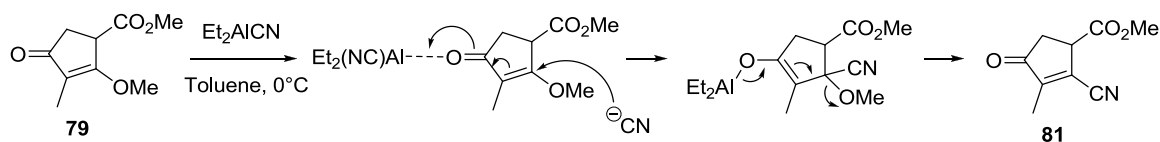
⁷⁴ Schulé, A.; Liang, H.; Vors, J. P.; Ciufolini, M. A. *J. Org. Chem.* **2009**, 74, 1587.

⁷⁵ Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, 24, 5425.



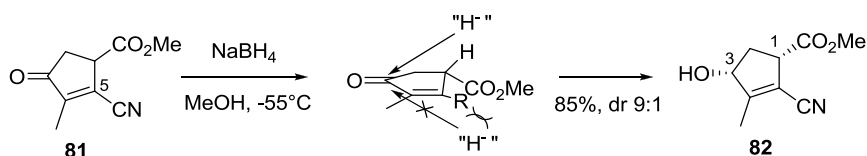
Scheme 22. Kinetic vs. thermodynamic enolate methoxycarbonylation.

1,4-Cyanation of enone **79** could then be performed using Nagata's reagent⁷⁶ (diethylaluminium cyanide). The Lewis acidity of the reagent simultaneously activates the C-2 carbonyl as well as being a source of the cyanide anion. The presence of a leaving group (OMe) allows the resultant enolate to regenerate the enone functionality in nitrile **81** (Scheme 23).



Scheme 23. Lewis acid mediated 1,4-cyanation.

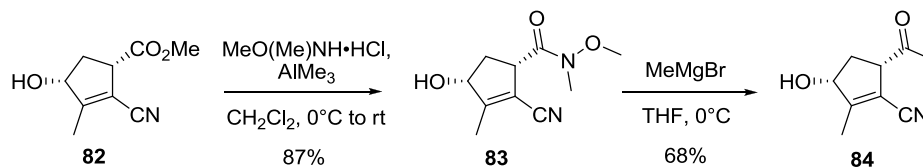
Diastereoselective reduction to alcohol **82** is performed using sodium borohydride at low temperature in order to avoid further reduction of the ester functionality. The relative steric hindrance of the C-5 position favours the 1,2 reduction, while the steric bulk of the ester below the face of the cyclopentenone directs the incoming hydride source to the opposite face, accounting for the diastereoselectivity in favour of the major 1,3-*cis* product (Scheme 24).



Scheme 24. Diastereoselective 1,2 reduction of enone **81**.

⁷⁶ Nagata, W.; Yoshioka, M. *Tetrahedron Lett.* **1966**, 7, 1913.

Once alcohol **82** was converted to the corresponding Weinreb amide **83**, the diastereomers could be separated with conventional column chromatography, and a final addition of methylmagnesium bromide furnished the allylation precursor ketone **84** (Scheme 25).

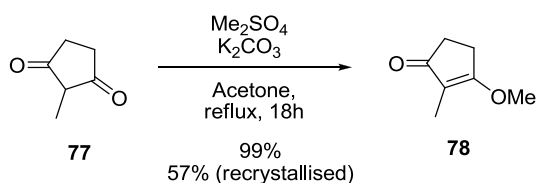


Scheme 25. Synthesis of ketone **84** avoiding overaddition.

2.2 Synthesis of allylation precursors

2.2.1 Regioselective alkoxy carbonylation

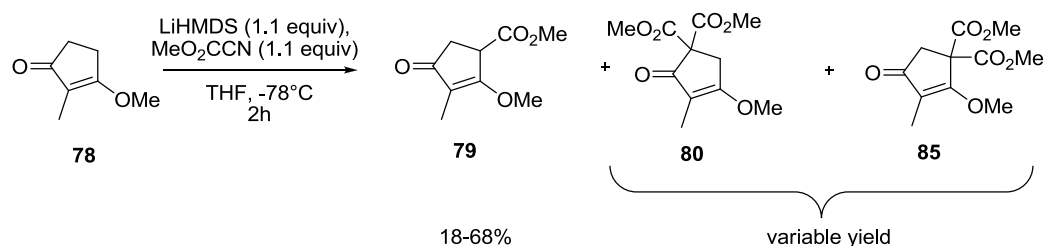
To start the synthesis, methyl enol ether **78** was generated from diketone **77** in quantitative yield. Although the crude material had acceptable purity as measured by ^1H NMR spectroscopy, it was possible to recrystallise the product from cyclohexane (Scheme 26).



Scheme 26. Enolate methylation.

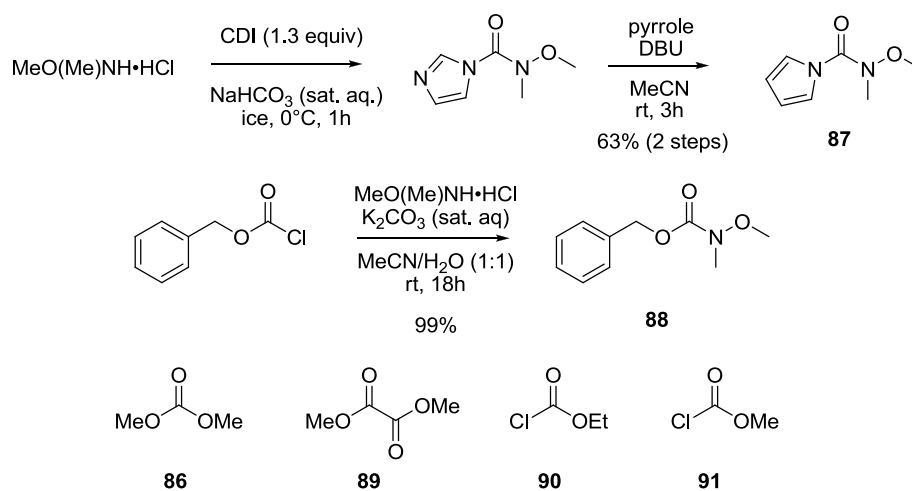
Deprotonation and methoxycarbonylation using Mander's reagent proved to be more difficult than previously indicated, however, with variable and non-reproducible yields. On larger scale especially, the yield dropped far below 50% (Scheme 27), with side products **80** and **85** and other unidentified minor products becoming more significant and often inseparable even through multiple chromatographic purifications. The generation of double addition products implies the formation of LiCN in the reaction mixture, but attempts to take advantage of this in order to install the required C-5 nitrile under the reaction conditions using Lewis acids proved fruitless. Mander's reagent has been documented to produce unwanted side-reactions in certain ketone substrates during attempts at C-

acylation, being sensitive to very specific reaction conditions.^{77,78} This limitation to scaling up and moving the synthesis forward led to a re-evaluation of this reaction.



Scheme 27. Regioselective methoxycarbonylation using Mander's reagent.

Different carbonyl electrophiles were investigated: dimethyl carbonate **86**,⁷⁹ Weinreb amides **87**⁸⁰ and **88**,⁸¹ dimethyl oxalate **89**,⁸² ethyl chloroformate **90**⁸³ and methyl chloroformate **91**.⁸⁴ Weinreb amides **87** and **88** first had to be synthesised from *N,O*-dimethylhydroxylamine (Scheme 28).⁸⁵ Table 2 summarises the results from the enolate addition to the various reagents.



Scheme 28. Various carbon electrophiles.

- ⁷⁷ a) Kazimierski, A.; Kałuza, Z.; Chmielewski, M. *ARKIVOC* **2004**, 2004, 213. b) Hale, K. J.; Grabski, M.; Flasz, J. T. *Org. Lett.* **2013**, 15, 370.
⁷⁸ Tomozane, H.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1988**, 36, 401.
⁷⁹ Kong, C.; Driver, T. G. *Org. Lett.* **2015**, 17, 802.
⁸⁰ a) Heller, S. T.; Newton, J. N.; Fu, T.; Sarpong, R. *Angew. Chem. Int. Ed.* **2015**, 54, 9839. b) Nugent, J.; Schwartz, B. D. *Org. Lett.* **2016**, 18, 3834.
⁸¹ Haydl, A. M.; Breit, B. *Chem. Eur. J.* **2017**, 23, 541.
⁸² Zhao, S.; Wei, P.; Wu, M.; Zhang, X.; Zhao, L.; Jiang, X.; Hao, C.; Su, X.; Zhao, D.; Cheng, M. *Bioorganic Med. Chem.* **2018**, 26, 3242.
⁸³ Corbu, A.; Perez, M.; Aquino, M.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2008**, 10, 2853.
⁸⁴ Boissel, V.; Simpkins, N. S.; Bhalay, G.; Blake, A. J.; Lewis, W. *Chem. Commun.* **2009**, No. 11, 1398.
⁸⁵ Nugent, J.; Schwartz, B. D.; Road, D. Y. *Org. Synth* **2017**, 94, 184.

Table 2. Acylation attempts.

Entry	Electrophile	Temp (°C)	Time (h)	Yield (%) (A:B:C)
1	86	-78 to rt	24	nr
2	87	-78 to rt	24	nr
3	88	-78 to rt	24	nr
4	89	-78 to rt	24	nr
5	90	-78 to 0	2	67 (3:0:1)
6	91	-78 to 0	2	77 (3.5:1:0)
7^a	91	-78 to 0	2	86 (>20:1:0)

a) Reverse addition.

Reactions with electrophiles **86-89** (Entries 1-4) did not produce any desired product even with extended reaction times, and would possibly require even more forcing conditions to proceed. However, the use of chloroformates **90** and **91** (Entries 5-7) gave exclusive C-alkoxycarbonylation. Although chloroformates commonly lead to O-acylation with ambident enolates, a number of factors contribute to the C-acylation exhibited. The small lithium cation is less electropositive compared to Na⁺ or K⁺, leading to a more covalent character of the Li-O bond, and consequently a reduced nucleophilicity of the oxygen atom. Empirical evidence suggests that tightly bound ion pairs and higher aggregates lead to increased C attack.⁸⁶ The use of lower polarity solvents such as THF favours the Li-O ion pairing leading to the formation of higher aggregates. Although the low temperature is not likely to lead to higher aggregates,⁸⁷ it, along with reverse addition, does control the deprotonation of the resulting product by unreacted enolate which would lead to over-addition of methyl chloroformate, although a slow raising of the temperature to 0°C is still required to drive the reaction to completion. Finally, the presence of a methoxy substituent at the β-position of **78** is expected to enhance the γ-acylation of dienolates due to added

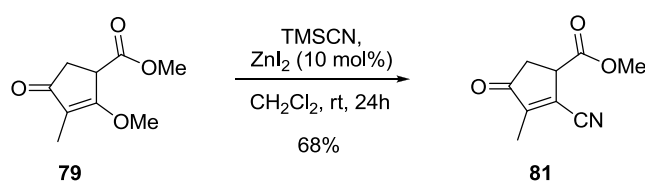
⁸⁶ Mayr, H.; Breugst, M.; Ofial, A. R. *Angew. Chem. Int. Ed.* **2011**, 50, 6470.

⁸⁷ Liou, L. R.; McNeil, A. J.; Ramirez, A.; Toombes, G. E. S.; Gruver, J. M.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, 130, 4859.

electron density as the γ -reaction site,⁸⁸ where normally the greater electron density lies at the α -position of dienolates of α,β -unsaturated ketones, leading to α -alkylation/acylation.⁸⁹

2.2.2 Selective enone reduction

1,4-Cyanation of enone **79** using Nagata's reagent was practically difficult; a commercial supply was not available and synthesis of the reagent is highly hazardous.⁹⁰ Fortunately the use of TMSCN in combination with a Lewis acid⁹¹ to mimic the dual role of Nagata's reagent was amenable to reproducible large scale synthesis (Scheme 29).



Scheme 29. Alternative cyanation procedure.

2.2.2.1 Diastereoselective enone reduction

Previous results indicated good diastereoselectivity when reducing nitrile **81** at low temperature with NaBH_4 to alcohol **82**. However, it was not possible to reproduce this result and the reaction consistently produced a lower diastereomeric ratio of 4:1, even at higher temperatures (Table 3, entries 1-3). Luche reduction conditions (Entry 4) produced an equal mixture of diastereomers, while milder or bulkier hydrides failed to react or caused extensive degradation (Entries 5 and 6), presumably from over-reduction and competing 1,4-conjugate reduction although the side products could not be identified. Finally, it was decided to move forward with the inseparable diastereomeric mixture (4:1) obtained at lower temperatures (Entry 7) to improve reproducibility and overall yield by minimizing over-reduction of the ester functionality.

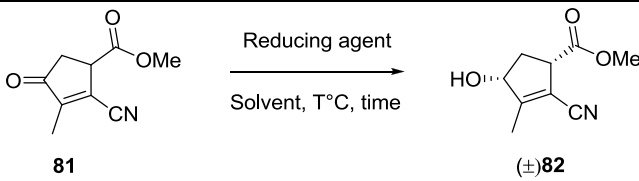
⁸⁸ Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.

⁸⁹ Djerassi, C.; Osiecki, J.; Eisenbraun, E. J. *J. Am. Chem. Soc.* **1961**, *83*, 4433.

⁹⁰ Nagata, W.; Yoshioka, M. *Org. Synth.* **1972**, *52*, 90.

⁹¹ Daiichi Pharmaceutical Co. Ltd. "IMIDAZO(1,2-a)PYRIDINE DERIVATIVE", European Patent 1479681A1, **2004**.

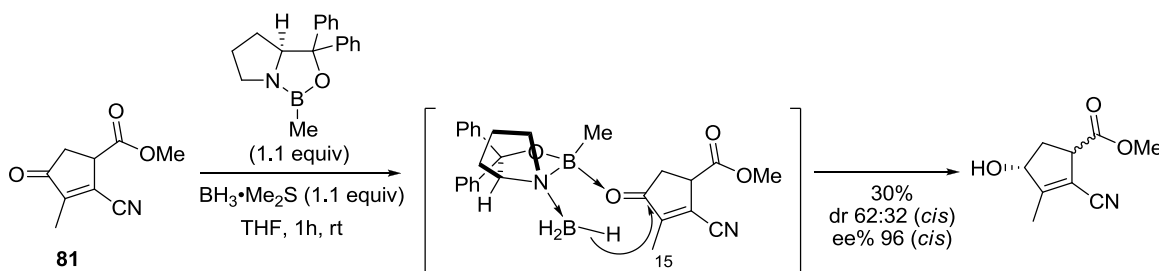
Table 3. Reduction of **81**.

						
Entry	Reducing agent	Solvent	Temp (°C)	Time	Yield (%)	d.r. (<i>cis:trans</i>)
1	NaBH ₄	MeOH	-55	1h	46	3.5:1
2	NaBH ₄	MeOH	-42	1h	70	4:1
					quant ^a	5:1 ^b
3	NaBH ₄	MeOH	-10		quant ^a	3:1
4	NaBH ₄ , CeCl ₃	MeOH	-78	30 min	quant ^a	1:1
5	Na(CH ₃ COO) ₃ BH	AcOH/CH ₂ Cl ₂ (1:1)	rt	2h	n.r.	n.r.
6	L-selectride	THF	-78	2h	0	n/a
7	NaBH₄	MeOH	-78	1h	93	4:1

a) crude yield. b) only on 0.558 mmol scale.

2.2.2.2 Enantioselective enone reduction

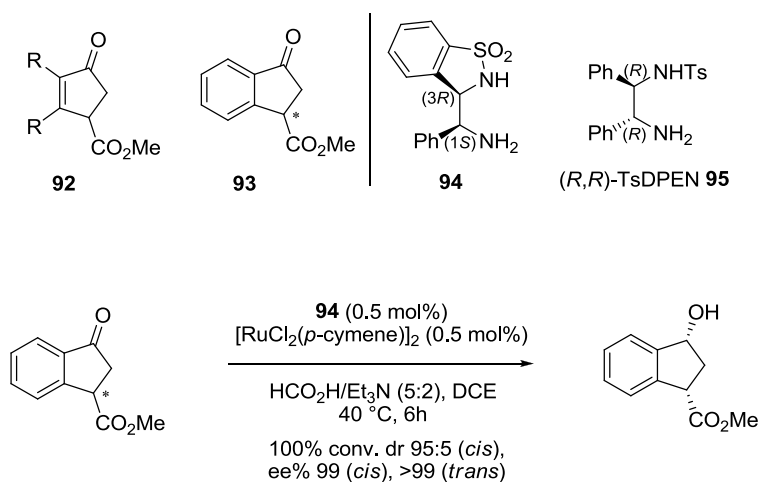
A preliminary investigation into the asymmetric reduction of nitrile **81** by Férézou *et al.* revealed that the Corey-Bakshi-Shibata (CBS) reagent could be used to reduce the enone carbonyl with good to excellent enantioselectivity, but unfortunately with little control over the diastereoselectivity (Scheme 30).^{72,92}

**Scheme 30.** CBS reduction of nitrile **81**.

To date only one previous report has been published concerning the catalytic asymmetric reduction of 5-membered γ -keto esters **92** (Scheme 31). The ruthenium(II)-catalysed

⁹² Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, 37, 1986.

asymmetric transfer hydrogenation (ATH) of *rac*-3-methoxycarbonyl-1-indanone **93** by Mohar *et. al.* proceeded with excellent diastereoselectivity and enantioselectivity when performed under dynamic kinetic resolution (DKR) conditions using γ -sultam-core ligand **94**⁹³, which is based on the conventional Noyori 1st generation TsDPEN ligand **95**.⁹⁴

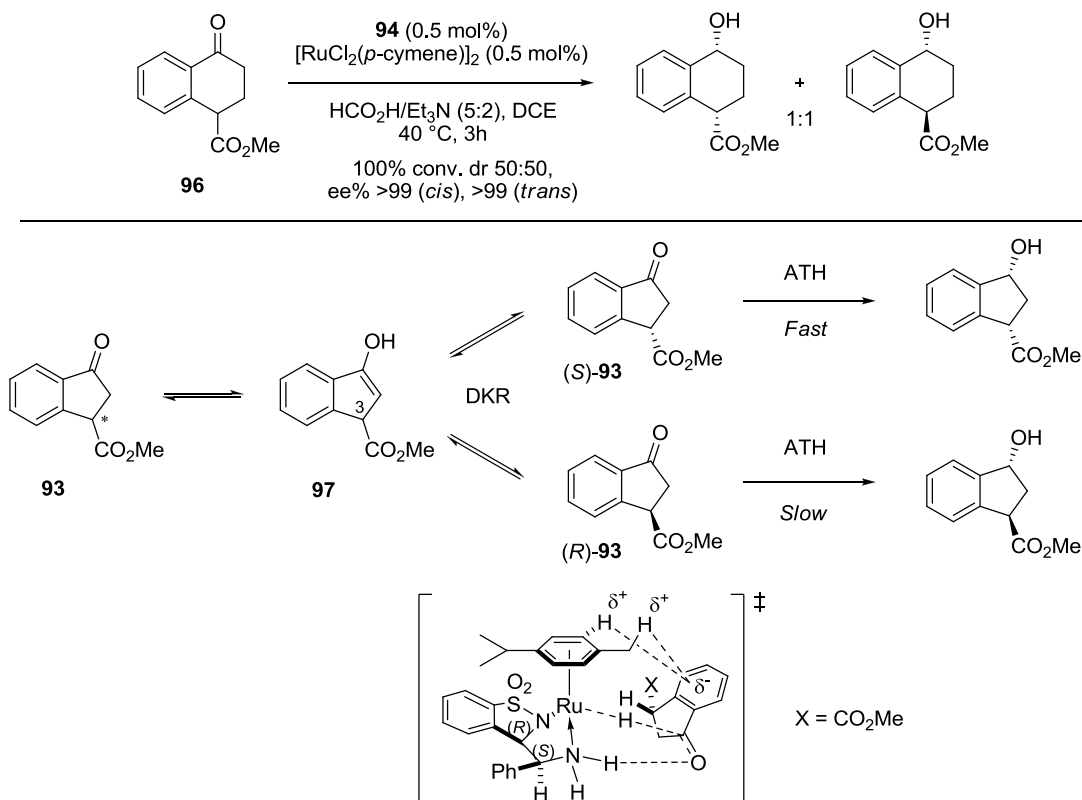


Scheme 31. Substrates and ligands for Ru(II)-catalysed ATH-DKR.

By observing that δ -keto ester **96** produced equal mixtures of diastereomers and therefore did not undergo racemisation under the reaction conditions they postulated that 1-indanone **93** underwent DKR by epimerisation of C-3 *via* the benzylic/allylic position of enol-tautomer **97** (Scheme 32).

⁹³ Rast, S.; Modéc, B.; Stephan, M.; Mohar, B. *Org. Biomol. Chem.* **2016**, *14*, 2112.

⁹⁴ Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.



Scheme 32. ATH-DKR of keto esters **96** and **93**.

The transition state based on previous calculations for Ru(II)-ATH (Scheme 32)⁹⁵ shows that the diastereoselectivity arises from *si*-face attack onto (*S*)-**93**. The (*S*)-enantiomer is preferentially reduced because the steric bulk of the ester is pointing outward away from the bulky diamine ligand. This is further helped by a favourable electrostatic interaction between the partial positive charge of the *p*-cymene C-H hydrogens and the substrate's electron-rich aromatic π -system. Applying this rationale to nitrile **81** however would necessitate a change in ligand. A reasonable assumption can be made that the phenyl ring in keto ester **93** is planar in nature and does not clash with the diamine phenyl rings. However, when using nitrile **81**, although the nitrile can be assumed to be planar and similarly sterically undemanding, the C-15 methyl hydrogens would be expected to interfere with the **94** diamine phenyl (Figure 10). Using Noyori's original (*R,R*)-TsDPEN ligand, this interaction on the *si*-face of the (*S*)-enantiomer can be minimised and therefore this ligand would be expected to produce the desired product (3*S*,1*R*)-**82** selectively.^{96,97} This is not the case with both faces of the (*R*)-enantiomer, where the C-15 methyl and the

⁹⁵ Dub, P. A.; Ikariya, T. *J. Am. Chem. Soc.* **2013**, *135*, 2604.

⁹⁶ Vidal, V. *private communication*.

⁹⁷ Sandoval, C. A.; Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Noyori, R. *Chem. Asian J.* **2006**, *1*, 102.

C-1 ester produce unfavourable interactions in the *re* and *si*-face respectively, the result being a slow hydrogen transfer reaction.

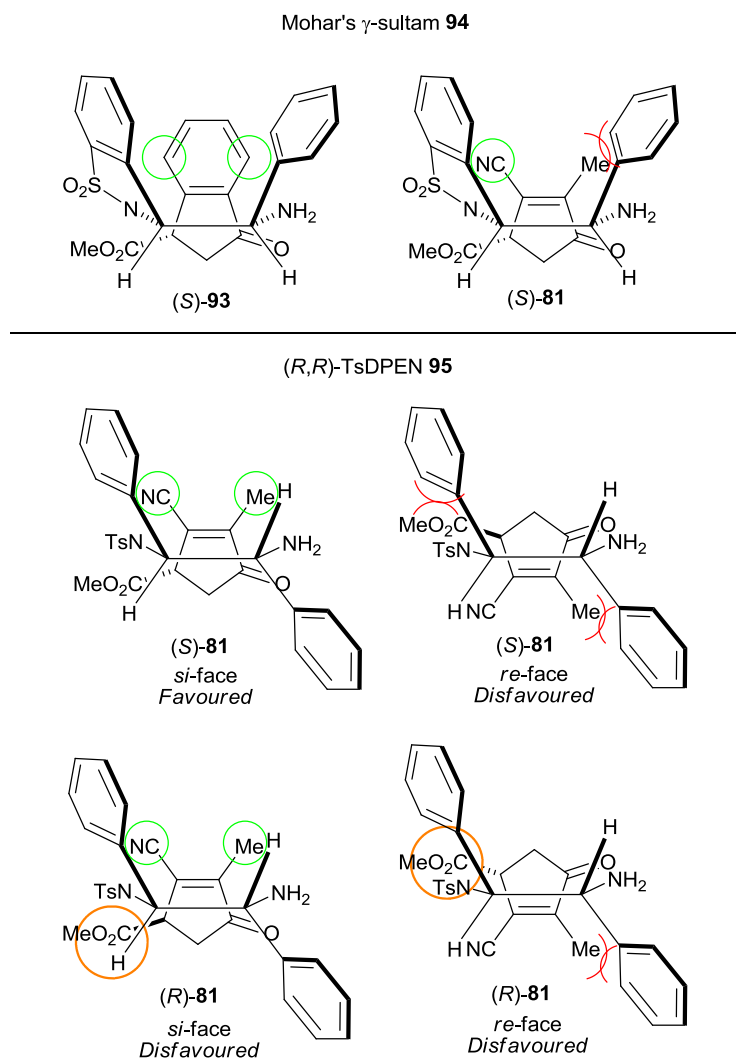
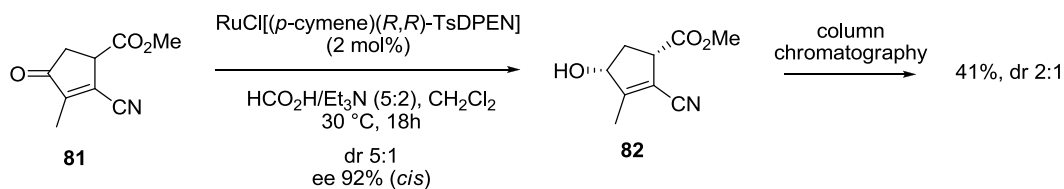


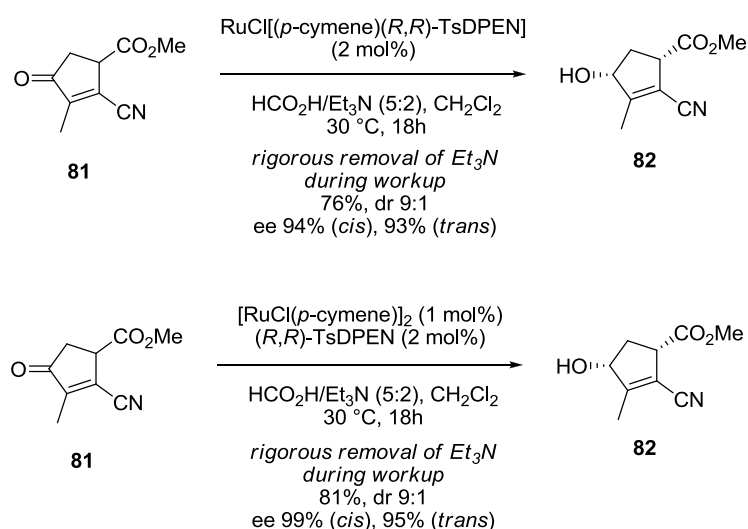
Figure 10. Ligand-substrate steric interactions for **81** and **93**. Ru(II) and *p*-cymene omitted for clarity.

Indeed this is the case; when the reaction was carried out with the commercially available $\text{RuCl}[(p\text{-cymene})(R,R)\text{-TsDPEN}]$ complex in the presence of a transfer hydrogenation source the reduction of **81** went to completion in 18 hours with good enantiomeric excess (Scheme 33), as determined by HPLC of the crude product.



Scheme 33. Trial reaction using ATH-DKR.

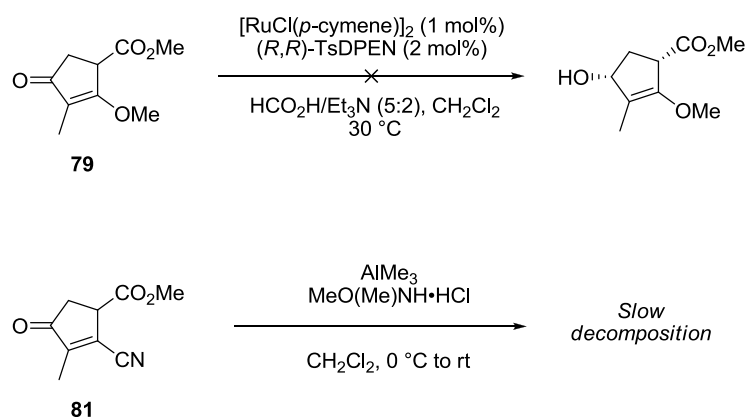
This proof of concept was encouraging, but after purification a reduced diastereomeric ratio was always encountered. Assuming that the reaction conditions were sufficient to epimerise the C-3 position *in situ* and that almost if not all formic acid was removed during aqueous workup, then residual triethylamine could be reasonably expected to cause epimerisation of the product in combination with silica gel. Rigorous removal of triethylamine during workup increases the diastereomeric ratio not only in the crude product after removal of volatiles but also in the final product after purification (Scheme 34).



Scheme 34. Optimisation of ATH-DKR.

By forming the catalyst *in situ* from the $[\text{RuCl}(p\text{-cymene})]_2$ dimer and $(R,R)\text{-TsDPEN}$ **95** and rigorously removing adventitious water from the solvent system beforehand, the reaction could be optimised to give good yields and excellent enantiomeric excesses; there was no reactivity difference even when performed on decagram scale. Presumably the remaining *trans* diastereomer arises from the weakly disfavoured steric interaction of the ligand with the *si*-face of $(R)\text{-81}$ (Figure 10); although the C-3 ester is now facing inwards towards the catalytic site, it does not directly clash with one of the diamine phenyl substituents. Similarly, the lower enantiomeric excess exhibited by the *trans* diastereomer can be explained by the disfavoured *re*-face of $(R)\text{-81}$, where the steric penalties can be expected to be slightly lower than that of the *re*-facial hydrogenation of $(S)\text{-81}$ as the ester is now pointing outwards.

A few attempts to explore the generality of ATH on α,β -unsaturated γ -keto esters with the TsDPEN ligand **95** met with failure (Scheme 35). No reaction was observed with ketoester **79** under the reaction conditions; presumably, the electron-donating β -OMe substituent either raises the reduction potential above that of the catalytic system, as electron-rich ketones are known to generally be poor substrates under Noyori ATH conditions⁹⁸ or enone **79** introduces steric incompatibility into the transition state, according to Figure 10, in a way that nitrile **81** does not. Attempts to generate the Weinreb amide analogue of **81** for testing were unsuccessful (Scheme 35 and Table 2, Entry 2) as direct conversion of the ester resulted in slow decomposition.



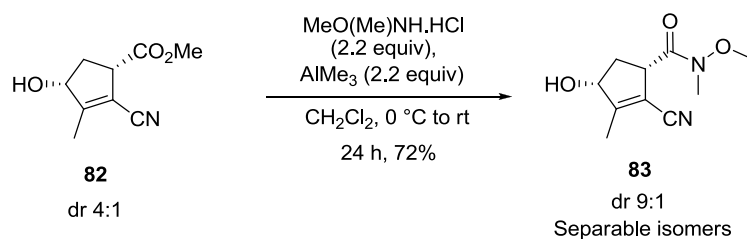
Scheme 35. ATH of methyl enol ether **79** and attempted amidation of ester **81**.

2.2.3 Weinreb amide synthesis

Although the conversion of ester **82** to its Weinreb amide according to previous conditions was not problematic (Scheme 36),⁹⁹ a consistent outcome was noticed whereby the diastereomeric ratio of the starting material (dr 4:1 *cis*) changed during the course of the reaction and generated a product with an increased diastereomeric ratio (dr 9:1 *cis*) without recovery of either starting materials or identifiable byproducts. The diastereomers of ester **82** are not separable by standard chromatographic means, and although Weinreb amide **83** can be separated from the accompanying *trans* diastereomer, it is a difficult separation that often requires several chromatographic separations before a sufficiently pure product is obtained, thus the reason for this diastereomeric enrichment is of clear interest.

⁹⁸ Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, 30, 97.

⁹⁹ Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 18, 4171.



Scheme 36. Weinreb amide formation driven to completion.

Under normal conditions, the reaction takes around 18-24 hours to completely consume the starting material. Reducing the equivalents of hydroxylamine salt and activating agent trimethylaluminium and analysing reaction aliquots at a halfway time interval *via* NMR allows for useful insights into the reaction mechanism (Figure 11). The diagnostic peak for the diastereomeric ratio of **82** is that of the proton at C-3 (*cis* = δ 4.56 ppm, *trans* = δ 4.91 ppm), as it is distinct in each diastereomer as well being separated from other protons. The conversion of *cis*-**82** is fast compared to the that of *trans*-**82** as evidenced by the decreasing diastereomeric ratio over time of the starting material and initial exclusive formation of *cis*-**83**. After 4 hours the conversion stalled according to TLC analysis and essentially pure *cis*-**83** was present according to NMR analysis of the crude material and could be isolated without laborious chromatographic diastereomer separation.

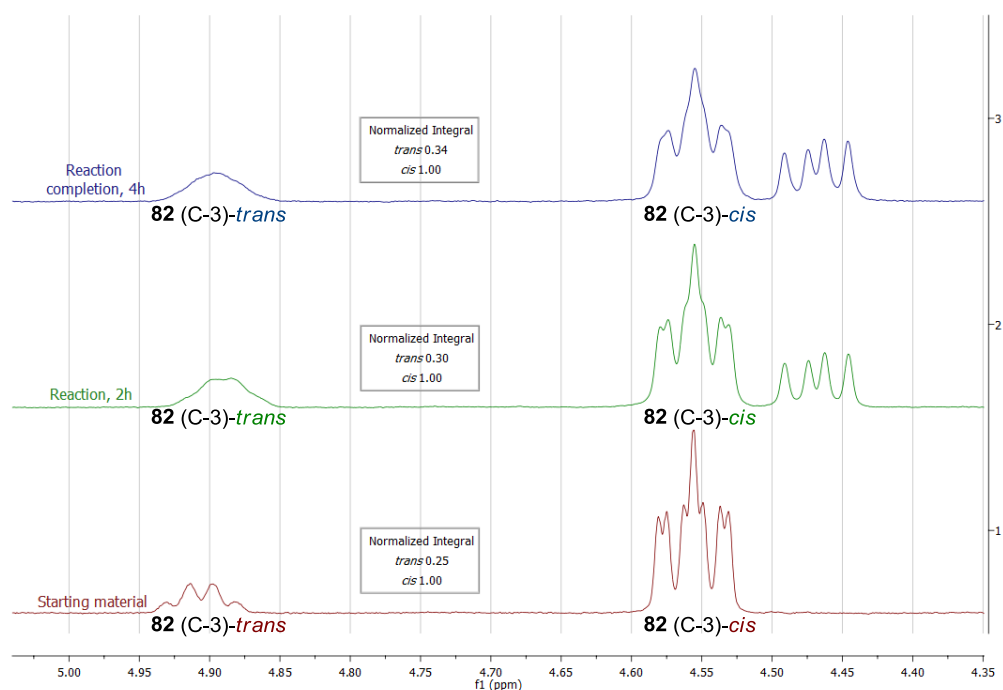
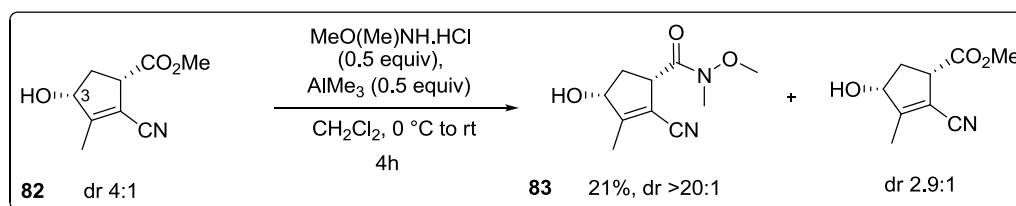
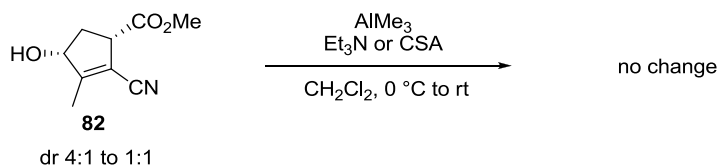


Figure 11. NMR analysis of the sub-stoichiometric conversion of ester **82** to amide **83**.

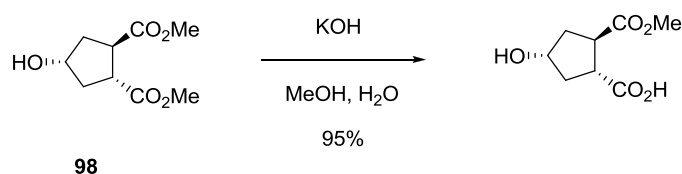
Because these reactions were performed on the racemic ester **82**, attempts were made to check that an *in situ* epimerisation was not occurring under the reaction conditions (Scheme 37). Subjecting the starting material of varying diastereomeric ratios to various conditions did not however result in any change.



Scheme 37. Epimerisation conditions.

An explanation for this behaviour would likely be due to the assistance of the C-3 hydroxyl group; the *cis* configuration allows for a relatively close proximity to the C-1 ester when compared to *trans*-**82**. Many such examples of hydroxyl-assisted ester reactivity exist, especially for saponification reactions, for instance the selective saponification of the *cis*-

ester in diester **98** during the total synthesis of macrolide antibiotic (\pm)-brefeldin A by Yamaguchi (Scheme 38).¹⁰⁰



Scheme 38. Selective saponification during the total synthesis of (\pm)-brefeldin A.

Looking at a possible minimised structure (MM2, Chemdraw) of **82** and comparing it to a simplified Na⁺-bound alkoxide **99** (Figure 12), it can be seen that the ester carbonyl lone pairs can assist in the ion-pairing of sodium, which can be extended to the synthesis of amide **83** by the assumption that Lewis acid coordination is fast compared to amine substitution.

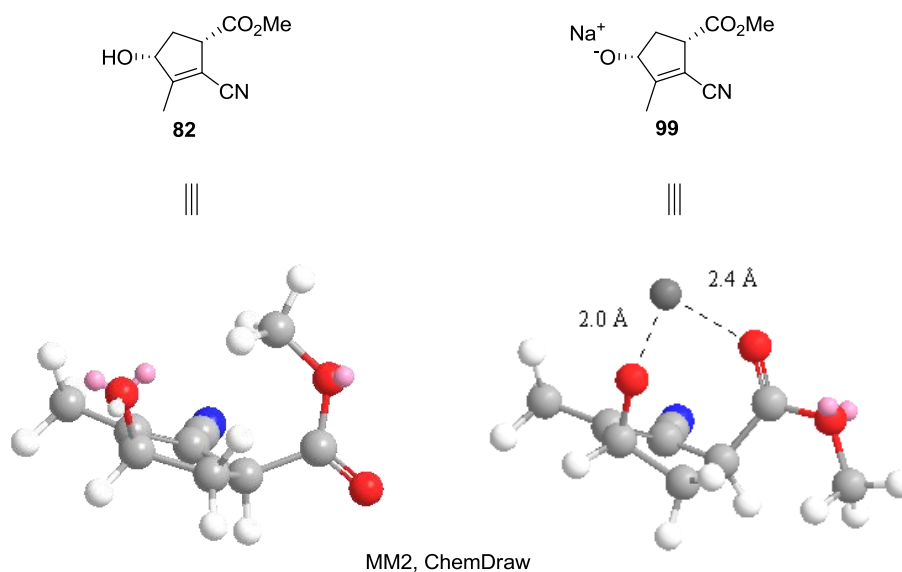
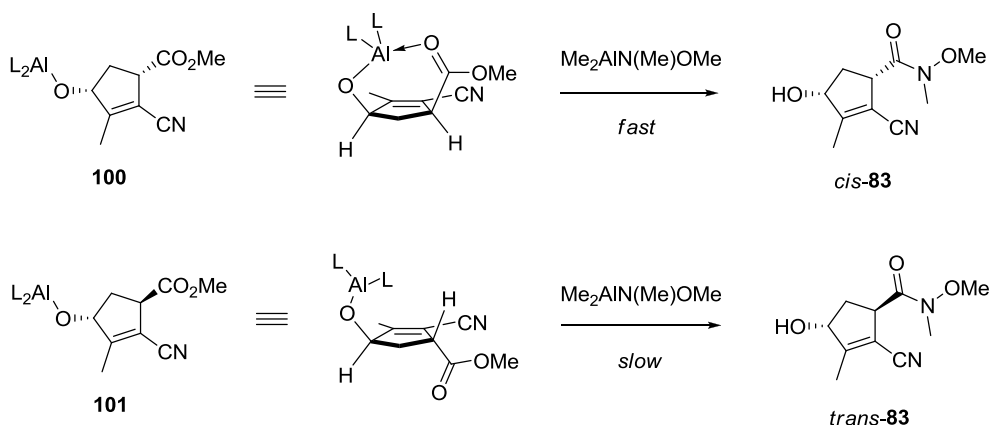


Figure 12. Minimisations of ester **82** and alkoxide **99**.

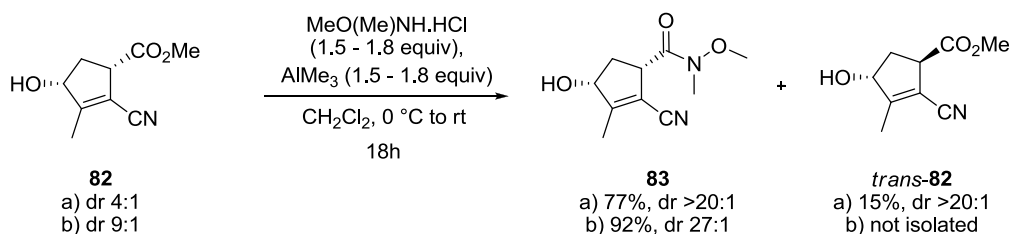
In the aluminium *cis*-complex **100** this means that the Lewis acid can now intramolecularly activate the C-1 ester for the conversion to Weinreb amide **83**, something which is not possible with aluminium complex *trans*-**101** (Scheme 39).

¹⁰⁰ Honda, M.; Hirata, K.; Sueoka, H.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1981**, 22, 2679.



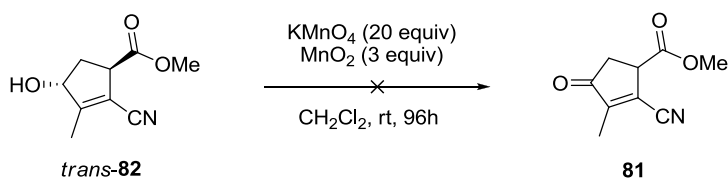
Scheme 39. Hydroxyl-assisted amide synthesis.

Based on this rationale, a set of optimised conditions can then be selected to take advantage of the faster reaction of *cis*-**82** (Scheme 40). After 18 hours, full conversion of *cis*-**82** is observed and *trans*-**82** can be recovered alongside the nearly diastereomerically pure product **83**. An adjustment to the reagent quantities has to be made according to the starting material diastereomeric ratio.



Scheme 40. Optimised conditions for Weinreb amide synthesis.

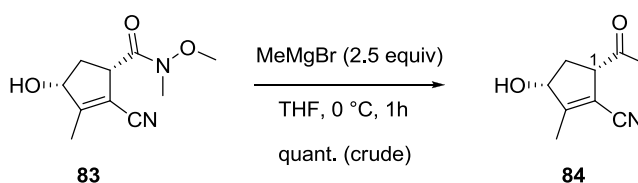
Although some attempts were made to recycle the isolated *trans*-**82** to the corresponding enone this was not successful, and because the remaining quantities of the *trans* alcohol after ATH-DKR were so low, this was not pursued further (Scheme 41).



Scheme 41. Allylic alcohol oxidation attempt.

2.2.4 Allylation ketone precursor

With the diastereomerically pure Weinreb amide **83** in hand, synthesis of the corresponding methyl ketone was straightforward. Addition of excess methylmagnesium bromide cleanly converted the amide to ketone **84** (Scheme 42).



Scheme 42. Synthesis of ketone **84**.

The ketone was not stable to standard, deactivated or pH neutral silica for chromatographic purification, and it epimerised easily at the C-1 position. Fortunately, it was found to be sufficiently pure to continue the synthesis using the crude product. Although the racemic crude ketone can be isolated as a yellow oil, addition of diethyl ether to crude (3*S*,1*R*)-**84** resulted in crystallisation. A sufficiently large single crystal could be grown *via* slow vapour diffusion and analysed by X-ray crystallography (Figure 13) in order to finally establish the absolute configuration produced by the earlier ATH-DKR experiments.

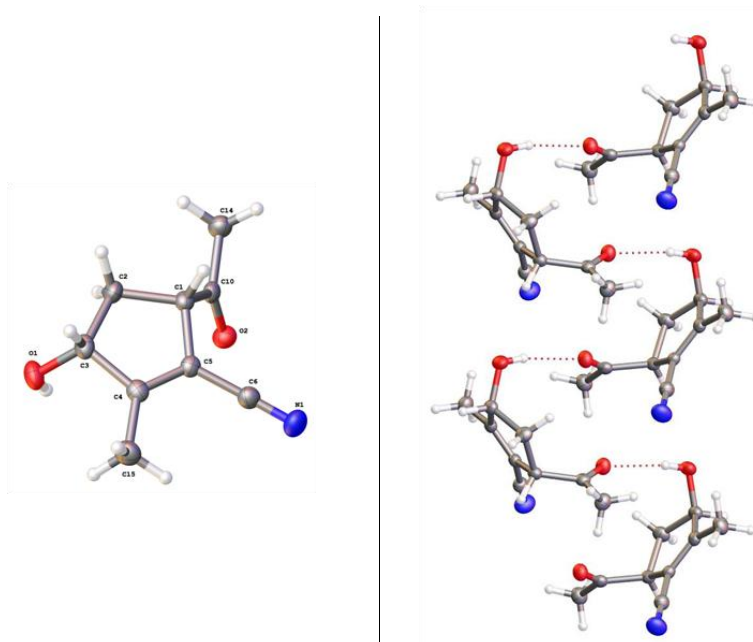
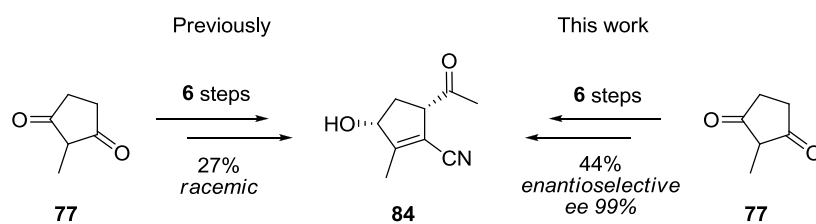


Figure 13. Single-crystal structure of **84**. Single unit and H-bonding interactions shown.

2.3 Conclusions

Ketone **84**, the precursor required for allylation, has been synthesised according to modified methodology from a previously established path. These modifications allowed reliable production of the highly enantioenriched synthetic intermediate **84** in decagram quantities in good to excellent yields, an outcome that compares favourably with previous results (Scheme 43).

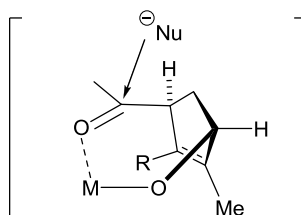
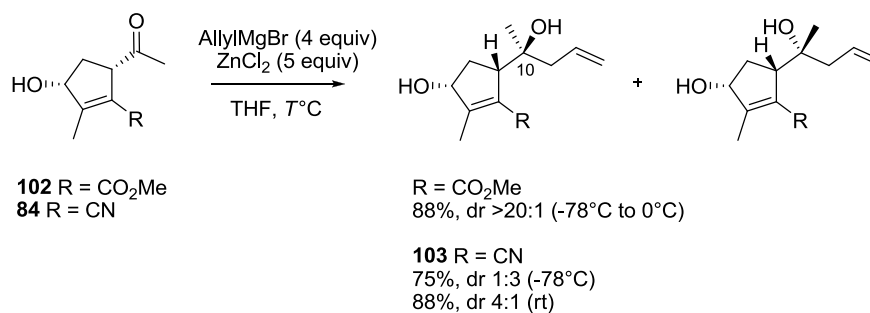


Scheme 43. Route comparison with previous attempts.

Chapter 3: Synthesis of the [5,7]-bicyclic core

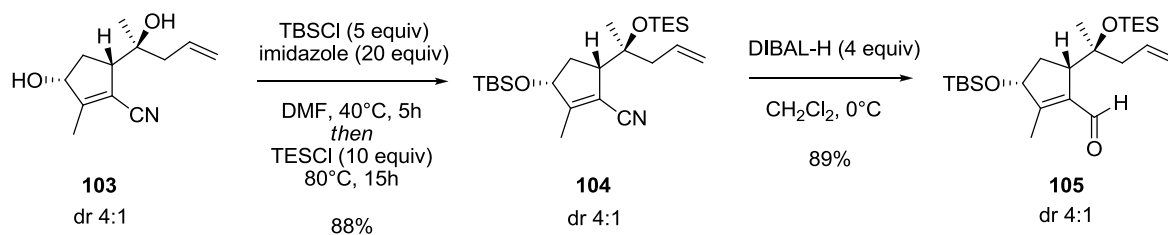
3.1 Previous work by Férézou *et al.*

Analogous to Ley's allylation approach of ketone **37** (Scheme 8), chelation-controlled Grignard addition to ketoester **102** proceeded with good yield and exclusive diastereoselectivity. Ketonitrile **84** exhibited a best-case diastereomeric ratio of 4:1 in favour of the desired diastereomer **103** when an excess of allylmagnesium bromide and zinc chloride was used (Scheme 44). This outcome was attributed to competing chelation effects of the C-3 alcohol and C-5 nitrile with the zinc-activated C-10 ketone which change with temperature. The inseparable mixture of diastereomers was carried through the rest of the synthesis.



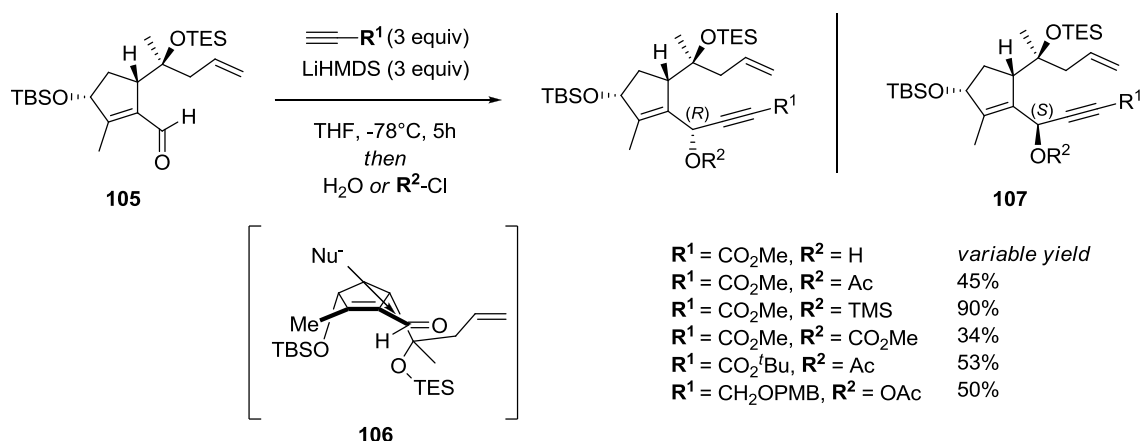
Scheme 44. Stereoselective allylation reactions.

One-pot sequential double hydroxyl protection of **103** followed by reduction of nitrile **104** with DIBAL-H furnished aldehyde **105** in good yield over two steps (Scheme 45). Later work also showed that mono-protection of the C-3 alcohol could allow the separation of the previously inseparable diastereomers.



Scheme 45. One-pot double-protection, and DIBAL-H reduction.

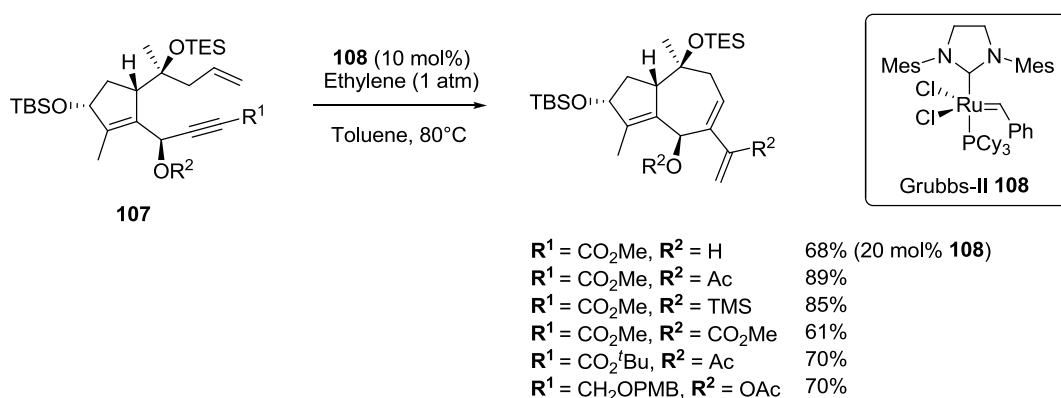
Alkynyl addition was accomplished by deprotonation of the corresponding terminal alkyne and addition of the resulting anion to aldehyde **105** at low temperature, followed by quenching of the resulting alkoxide with water or an electrophilic trapping agent (Scheme 46). Initial assignment of the resulting exclusive diastereomers by M. Jouanneau was done on the basis of nucleophilic attack on the minimal-energy conformer **106**, because corroborating evidence from NOE studies was difficult to obtain. Later work performed by R. Bonnepally involving NOE studies on more rigid cyclised derivatives suggested that the opposite diastereomer **107** had formed. This could be rationalised more appropriately by consideration of the more reactive conformer and this will be explored later in this chapter.



Scheme 46. Stereoselective alkynylation.

After a screening of some common metathesis conditions, the key ring-closing ene-yne metathesis step was accomplished on various substrates in toluene using 10 mol% of 2nd-generation Grubbs initiator **108** under elevated temperatures and an ethylene atmosphere (Scheme 47). These conditions were successful for all the substrates, although reaction of the substrate bearing free allylic alcohol was shown to be less efficient compared to those of protected analogues and required the use of 20 mol% of catalyst to deliver reproducible yields. In many cases an hydroxyl group proximal to the metathesis

site can increase reactivity in different types of metathesis reactions,¹⁰¹ but a full accounting for this particular case was not explored.

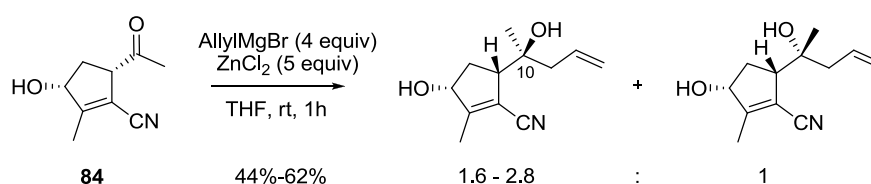


Scheme 47. Ring-closing ene-yne metathesis.

3.2 RCYEM precursors

3.2.1 Ketone allylation

Subjection of ketone **84** to the previous allylation conditions (Scheme 44) led to variable outcomes in many cases, mostly characterised by low yields and poor diastereoselectivities (Scheme 48). Due to the highly hygroscopic nature of the pre-dried ZnCl_2 , it is hard to rule out interference of moisture from the atmosphere, although the large excess of Grignard reagent which is mixed with the ZnCl_2 before the addition of the ketone substrate should minimize this.

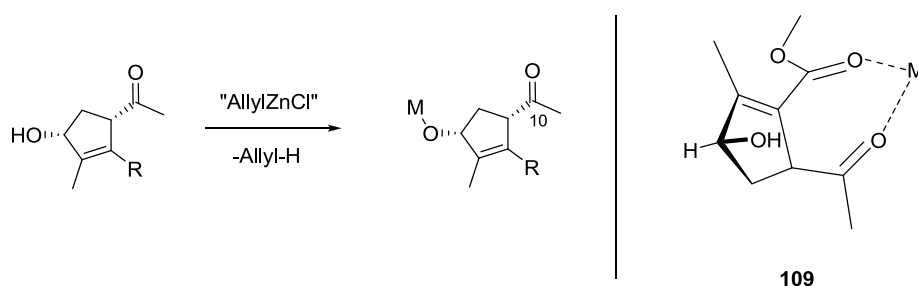


Scheme 48. Trial zinc-mediated allylations.

This barrier to efficient stereoselective access of the C-10 tertiary alcohol prompted a closer look at the reaction conditions. First, the rationale for transmetallation of the Grignard reagent with ZnCl_2 is that the high reactivity of allylmagnesium halides often

¹⁰¹ Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, 6, 1219.

leads to diastereoselectivity problems because the rates of reaction approach the limit of diffusion,¹⁰² whereas corresponding organozinc halides can show improved selectivity, although the reduced Lewis acidity of Zn(II) does not activate carbonyl compounds well.¹⁰³ The first assumption that can be made is that deprotonation of the free alcohol is much faster than nucleophilic attack (Scheme 49) and that this leaves an alkoxide-metal ion pair which can coordinate to the C-10 carbonyl. The large electron density surrounding the oxygen would then also be expected to largely eliminate any coordination competition with the C-5 nitrile. In addition, if chelation competition with a C-5 substituent was taking place, a similar chelation competition would be expected in ketoester **102** leading to complex **109**, which does not correspond to the observed outcome of near complete diastereoselectivity.



Scheme 49. Initial deprotonation and unlikely chelation competition in ketoester **102**.

The identity of M can be ambiguous, as the stoichiometric mixing of alkylmagnesium halides and zinc chloride is known to result in mixed magnesium-zinc alkyl halide species.¹⁰⁴ However, both Zn^{2+} and Mg^{2+} can form multicoordinate complexes, which is important to differentiate between ketonitrile **84** and ketoester **102**. Figure 14 shows a possible minimized interaction **110** (MM2, Chemdraw) of Mg^{2+} , Zn^{2+} , a bridging Cl^- (as Br^- is not expected to participate as a bridging anion) and the ketoester substrate. The alkoxide and both carbonyl groups are able to participate in coordination to the more oxophilic¹⁰⁵ Mg^{2+} and this leaves only the *si*-face accessible for nucleophilic attack, as evidenced by the high stereocontrol of this reaction at varying temperatures (Scheme 44).

¹⁰² Read, J. A.; Woerpel, K. A. *J. Org. Chem.* **2017**, 82, 2300.

¹⁰³ Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, 93, 2117.

¹⁰⁴ Hevia, E.; Chua, J. Z.; Garcia-Alvarez, P.; Kennedy, A. R.; McCall, M. D. *Proc. Natl. Acad. Sci.* **2010**, 107, 5294.

¹⁰⁵ Kepp, K. P. *Inorg. Chem.* **2016**, 55, 9461.

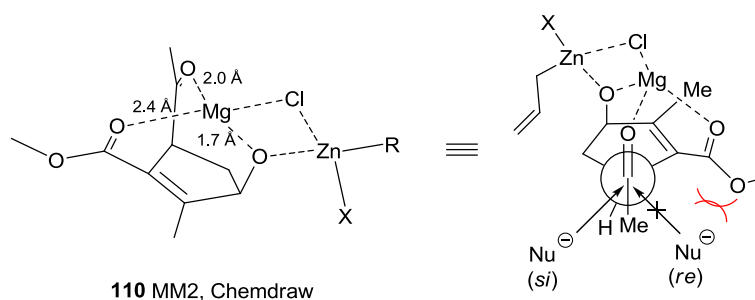


Figure 14. Possible configuration of chelate complex between mixed magnesium-zinc alkyl halides and ketoester **102**.

This type of dinuclear chelate complex **111** is widely invoked for the asymmetric alkylations of carbonyl compounds by alkyl magnesium/zinc reagents using chiral diols or amino alcohols to induce enantioselectivity (Figure 15). In this case, one metal centre is usually coordinated to the carbonyl while the other effects alkyl transfer to one face preferentially.¹⁰⁶

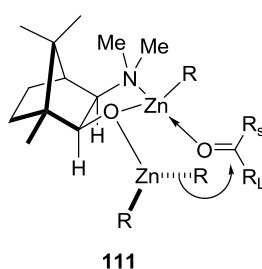


Figure 15. Asymmetric alkylation chelate complex involving two metal centres.

The tridentate nature of ketoester **102** is not present in ketonitrile **84**, and the smaller steric encumbrance of the "needle-like" C-5 nitrile both indicate that the *re*-face is now more accessible (Figure 16). Chelate complex **112** can also be expected to be more susceptible to variation in temperature compared to complex **110**, as the now internally coordinatively-unsaturated metal centre is not as rigidly positioned.

¹⁰⁶ Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, 30, 49.

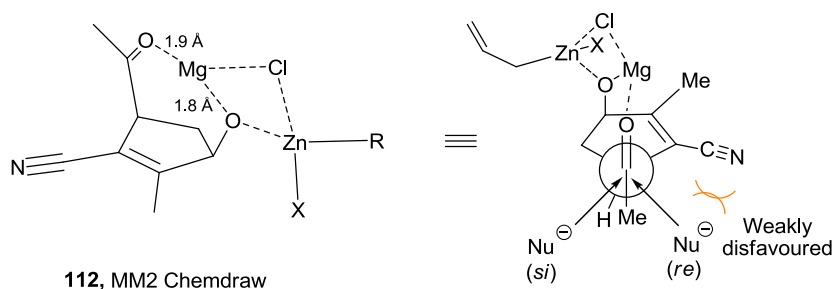
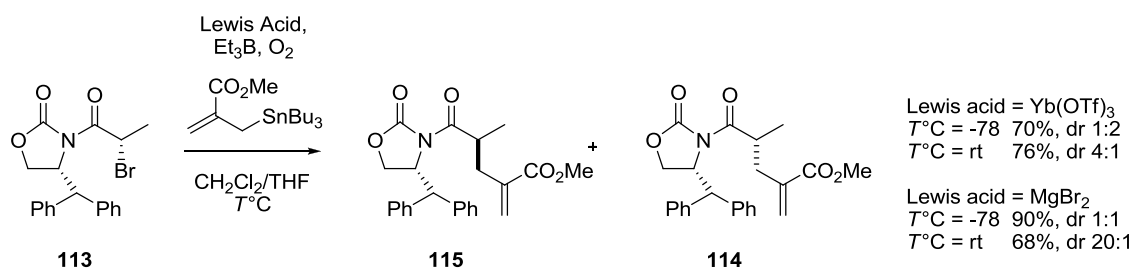


Figure 16. Possible configuration of chelate complex between mixed magnesium-zinc alkyl halides and ketonitrile **84**.

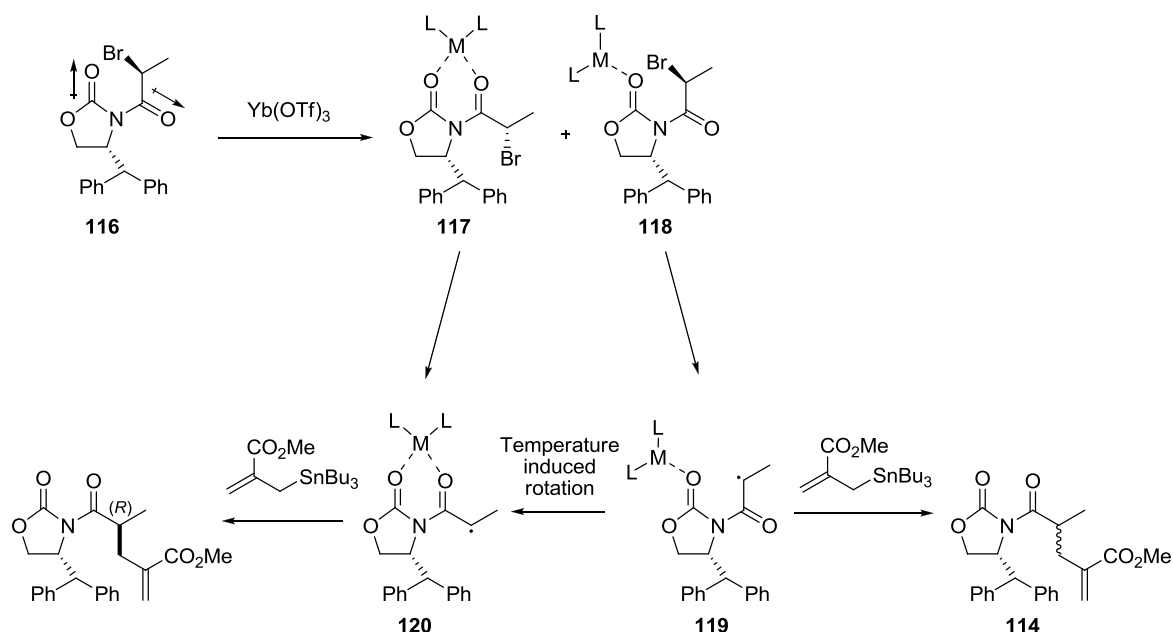
A similar temperature dependence was noticed by Sibi *et al.* during radical allylation reactions of α -bromooxazolidinone imides (Scheme 50).¹⁰⁷ The Lewis acid-mediated allylation of **113** at low temperature proceeded with a small selectivity in favour of the unexpected diastereomer **114**. An increase in the temperature led to the formation of the opposite diastereomer **115** as the major product.



Scheme 50. Temperature dependence of radical allylations.

Taking into account all their observations, they proposed the pathway laid out in Scheme 51. Without a Lewis acid, dipole-dipole minimized structure **116** is thought to exist predominantly, and only the portion of molecules that exist as rotamer **117** can adopt a Lewis acid chelate before radical generation. Mono-complexed rotamer **118** can still generate radical **190** which can proceed to product **114** with weak stereinduction in favour of the (*S*) configuration. At higher temperatures, bond rotation in radical **119** is more likely to form bidentate radical **120**, which leads to the desired (*R*) configuration **115**. The use of slower radical trapping agents to allow time for bond rotation and favour the (*R*)-configured product supported this explanation. It should also be noted that changing the nature of the chelating metal centre also had an effect on diastereoselectivity, attributed to changing steric interactions favouring chelation of MgBr₂ over that of Yb(OTf)₃.

¹⁰⁷ Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873.



Scheme 51. Temperature dependant allylation proposed pathway.

This predetermined conformation before Lewis acid involvement could be key to the selectivity of the allylation reaction of ketonitrile **84**. If, like before, the assumption is made that deprotonation of ketonitrile **84** is much quicker than allylation, then uncomplexed alkoxide **121** can play a large role in the selectivity, especially at low temperatures (Figure 17). In particular, a charge-dipole interaction can be considered part of the initial conformation after deprotonation. Analogous to the temperature dependence of Sibi's radical allylations, if the thermodynamic chelation control is not fully established at low temperatures, the *re* face might be expected to react with an allylating agent as a kinetic effect, leading to the observed reversed selectivity. The tridentate nature of ketoester **102** would be expected to enforce the chelated complex quicker due to the increased favourable electrostatic interactions.

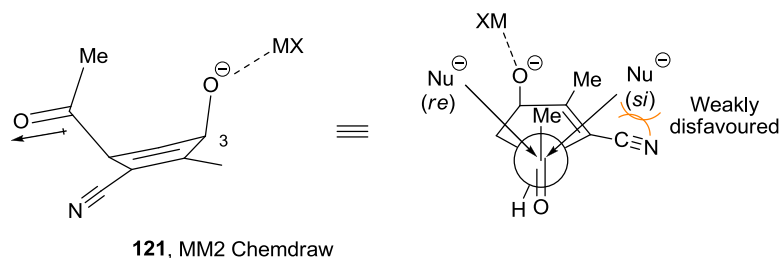
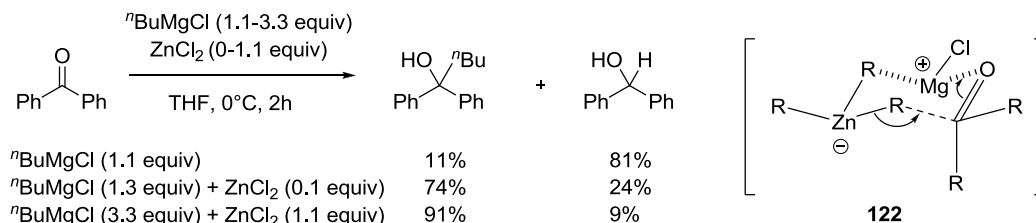


Figure 17. Possible conformation of the corresponding alkoxide of ketonitrile **84**.

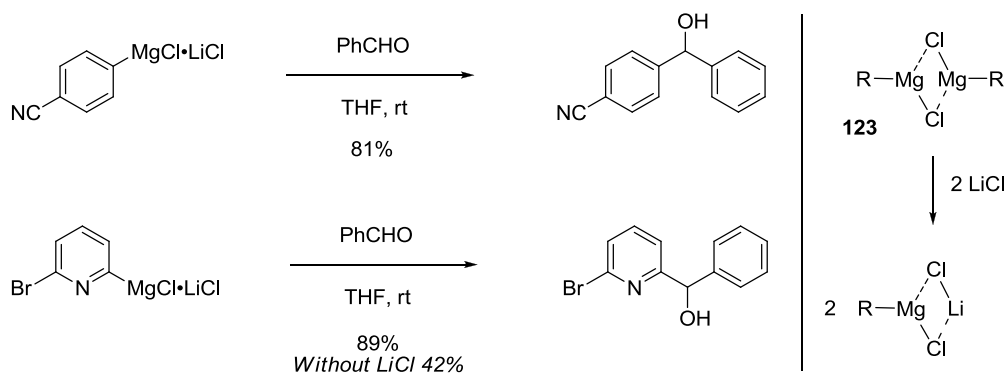
On this basis modifications can be made to the allylation reaction conditions in order to suit nitrile **84** better. Stoichiometric and catalytic amounts of zincates $[R_2Zn-R]^-$ have been

shown to add efficiently to a wide range of ketone substrates to yield the corresponding tertiary alcohols (Scheme 52).¹⁰⁸ In addition, the cyclic transition-state **122**, involving carbonyl activation by a $[\text{MgCl}]^+$ species, fits closely with proposed chelate model **112**.



Scheme 52. Zn(II)-ate mediated ketone alkylations.

The addition of LiCl to standard Grignard reagents in THF to form so-called "turbo-Grignard" reagents by Knochel has led to greatly enhanced reactivity and functional group tolerance in many cases (Scheme 53).¹⁰⁹ This has been proposed to occur through the breaking of polymeric aggregates **123** to give monomeric species due to the high polarity of Li^+ . This inclusion of Li^+ could be used in chelated complex **112** to effect faster chelation and avoid the involvement of complex **121**.



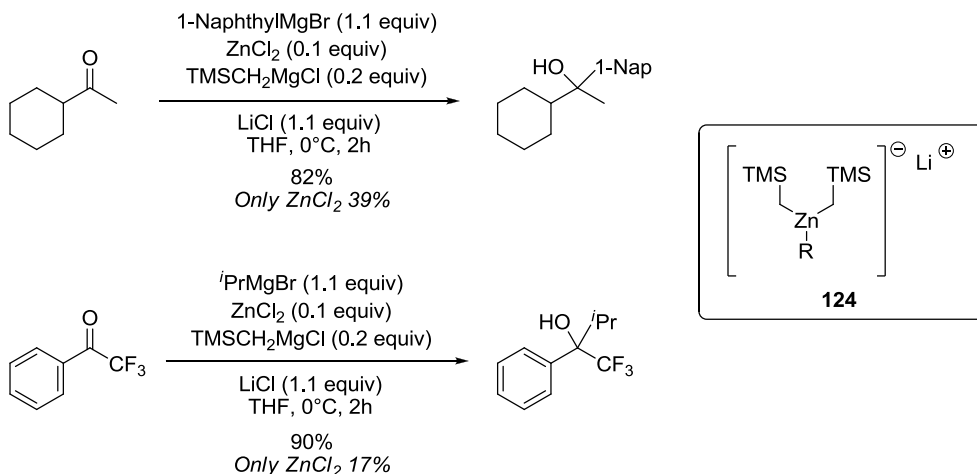
Scheme 53. Use of "Turbo Grignards" in sensitive substrates.

It is also possible to use zinc(II)-ate complexes to increase the steric bulk of the nucleophile. By first generating the catalytic Zn complex **124**, which includes two bulky non-transferable alkyl groups, from the corresponding starting Grignard reagent $\text{TMSCH}_2\text{MgCl}$, and subsequently using that complex to transfer alkyl nucleophiles to substrates, Hatano was able to efficiently alkylate difficult substrates that were prone to

¹⁰⁸ Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998.

¹⁰⁹ Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

hydride transfer and other side-reactions even with the previous inclusion of catalytic ZnCl_2 (Scheme 54).¹¹⁰ Additionally, these reactions could be performed with bromide and iodide Grignard reagents, which are easier to obtain because of the high propensity of Mg to insert into these C-X bonds, but are also less reactive alkylating reagents compared to RMgCl .

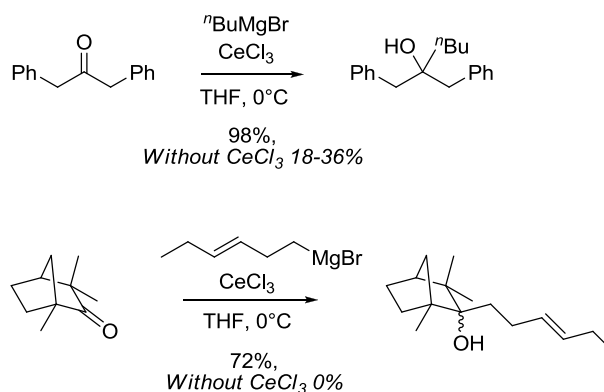


Scheme 54. Alkylation catalysed by Zn(II) -ate complexes bearing non-transferable ligands.

Finally, reagents generated by stoichiometric transmetallation of Grignard reagents with the highly oxophilic CeCl_3 have previously shown remarkable nucleophilicity and reduced basicity, resulting in highly selective addition of hindered nucleophiles and hindered/enolisable ketones (Scheme 55).¹¹¹ CeCl_3 exhibits a tendency to form chelated complexes with ketones, and could improve the low temperature chelation of ketonitrile **84**.

¹¹⁰ Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* **2010**, 46, 2674.

¹¹¹ Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, 111, 4392.



Scheme 55. Imamoto's CeCl_3 mediated alkylations.

Re-examination of temperature dependence in the original allylation conditions (Entries 1-3, Table 4) revealed no further improvement over ambient temperature. In fact, the reduction in yield of **103** in Entry 3 indicates that side-reactions occur more readily at higher temperatures with no improvement in diastereoselectivity. The chloride Grignard reagent (Entry 4) showed a decreased yield as well, possibly due addition reactions to the C-5 nitrile because of its higher reactivity.¹¹² The lithium chloride salt effect (Entries 5) also caused additional reactivity problems, creating a mixture of multi-allylated products. Stoichiometric and catalytic use of zinc(II)-ates (Entries 6 and 7) gave similarly disappointing reactivity issues. Hatano's alkylsilylzinc(II)-ate catalytic conditions did improve the yield when used in combination with allylmagnesium chloride (Entry 9) but the added steric bulk did not lead to better diastereoselectivity. The inherent high reactivity of these complexes meant that the reactions had to be run at -78°C in order to avoid competing side-reactions. Fortunately, the use of oxophilic alkylcerium reagents (Entries 10 and 11) provided consistent yields with superior stereocontrol. Avoiding the deactivation of CeCl_3 through hydrolysis during the drying of the cerium chloride hydrate proved key to successful reproducibility. The use of allylMgBr in this reaction leads to comparable yields and diastereomeric ratios.

¹¹² Allen, B. B.; Henze, H. R. *J. Am. Chem. Soc.* **1939**, *61*, 1790.

Table 4. Allylation of ketonitrile **84**.

	84		(10S)-103	(10R)-103	
Entry	RMgX	Additives	Temp (°C)	Yield (%)	S:R
1	AllylMgBr (4 equiv)	ZnCl ₂ (5 equiv)	rt	50	2.8:1
2	AllylMgBr (4 equiv)	ZnCl ₂ (5 equiv)	0	52	1.6:1
3	AllylMgBr (4 equiv)	ZnCl ₂ (5 equiv)	40	23	2.6:1
4	AllylMgCl (4 equiv)	ZnCl ₂ (5 equiv)	rt	40	3:1
5	AllylMgBr (4 equiv)	ZnCl ₂ (5 equiv)	rt	33	2:1
6	AllylMgCl (3 equiv)	LiCl (2 equiv)			
		ZnCl ₂ (1 equiv)	rt	5	3:1
7	AllylMgBr (3 equiv)	LiCl (2 equiv)			
		ZnCl ₂ (0.1 equiv)	rt	9	3:1
8	AllylMgBr (4 equiv)	ZnCl ₂ (0.1 equiv)	-78	44	2.2:1
		TMSCH ₂ Cl (0.2 equiv)			
		LiCl (2 equiv)			
9	AllylMgCl (4 equiv)	ZnCl ₂ (0.1 equiv)	-78	73	3:1
		TMSCH ₂ Cl (0.2 equiv)			
		LiCl (2 equiv)			
10^a	AllylMgCl (2.2 equiv)	CeCl₃ (2 equiv)	-78	88	4:1
11^b	AllylMgCl (2.2 equiv)	CeCl₃ (2 equiv)	-78	93	6:1

a) CeCl₃·7H₂O dried at 140 °C for 8h b) Careful drying of CeCl₃·7H₂O¹¹³

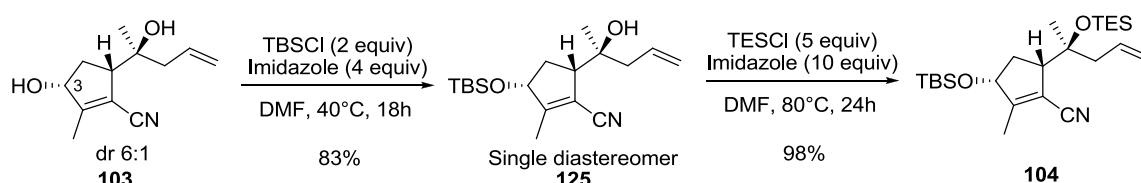
Therefore highly active cerium chlorides seemingly led to efficient chelation even at low temperature, helping to improve facial selectivity of incoming nucleophiles. The inseparable mixture of diastereomers was carried over into the next stage of the synthesis.

¹¹³ Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, 37, 6787.

3.2.2 Stereoselective alkynylation

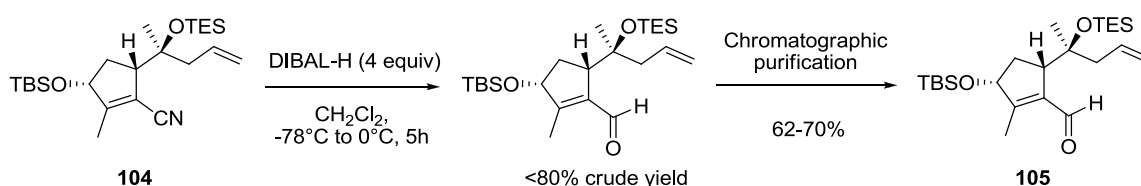
3.2.2.1 Alkynylation precursor

Selective TBS-protection of the C-3 alcohol led to mono-silylated alcohol **125**, which allowed separation of the allylation product diastereomers (Scheme 56). Protection of the tertiary C-10 alcohol as the triethylsilyl ether **104** proceeded in excellent yield and this silyl ether proved to be a very stable synthetic intermediate, as large quantities could be stored at ambient conditions for >6 months without obvious degradation.



Scheme 56. Sequential double silylation.

The selective reduction of nitrile **104** using excess DIBAL-H did proceed with high conversion to the presumed imine intermediate, but standard workup conditions for DIBAL reductions (Fieser method¹¹⁴ /Rochelle's salt) generally gave somewhat disappointing crude yields, exacerbated by large yield reductions during subsequent chromatographic purification (Scheme 57).



Scheme 57. Initial attempts at nitrile reduction.

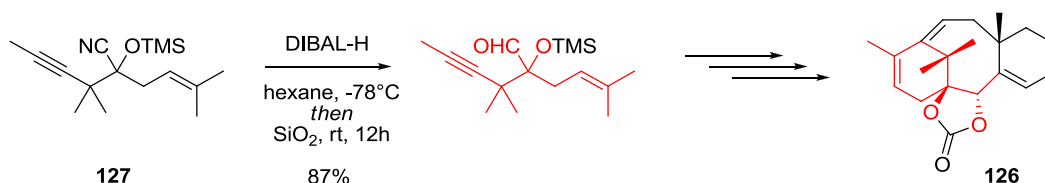
Mild imine hydrolysis has previously been used to good effect on sensitive substrates within the Prunet group during the synthesis of the tricyclic core **126** of taxol.¹¹⁵ Reduction

¹¹⁴ Ho, T.-L.; Fieser, M.; Fieser, L.; Danheiser, R.; Roush, W.; Smith, J. In *Fieser and Fieser's Reagents for Organic Synthesis*; John Wiley & Sons, Inc., **2013**, 253.

¹¹⁵ a) Letort, A.; Aouzal, R.; Ma, C.; Long, D. L.; Prunet, J. *Org. Lett.* **2014**, *16*, 3300.

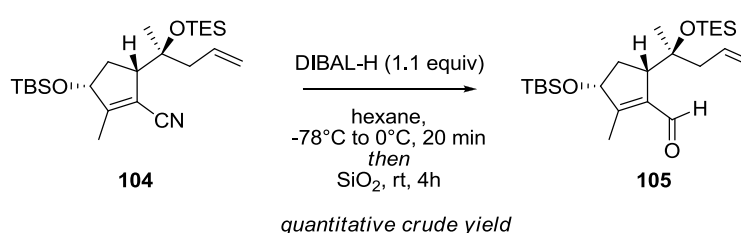
b) Letort, A.; Long, D. L.; Prunet, J. *J. Org. Chem.* **2016**, *81*, 12318.

of TMS-protected cyanohydrin **127** was carried out using DIBAL-H in hexane, after which the addition of silica gel facilitated the mild hydrolysis (Scheme 58).



Scheme 58. Nitrile reduction during synthetic efforts towards taxol.

Applying this strategy to nitrile **104** conveniently furnished the desired crude aldehyde **105** after DIBAL-H reduction by stirring with an amount of silica gel for up to 4 hours followed by simple filtration (Scheme 59). The crude aldehyde is recovered quantitatively and essentially pure by NMR and was therefore carried on into the next reaction without further purification.



Scheme 59. Improved nitrile reduction through mild imine hydrolysis.

3.2.2.2 Aldehyde alkynylation

As NOE studies had previously suggested the formation of the (*S*)-configured C-6 secondary alcohol during alkynylation of aldehyde **105**, it is likely that *cis*-**105** is the reactive conformer. An energy difference of approximately 2.3 kcal/mol (MM2, ChemBio3D) between the *cis* and *trans* conformers allows for an equilibrium with some *cis* character during the reaction. A rough estimate of the rotational energy barrier ($\Delta E^\circ \approx 5.0$ kcal/mol, MM2, ChemBio3, calculated at 1° intervals, Figure 18) then also allows for the rapid interconversion between both conformations.

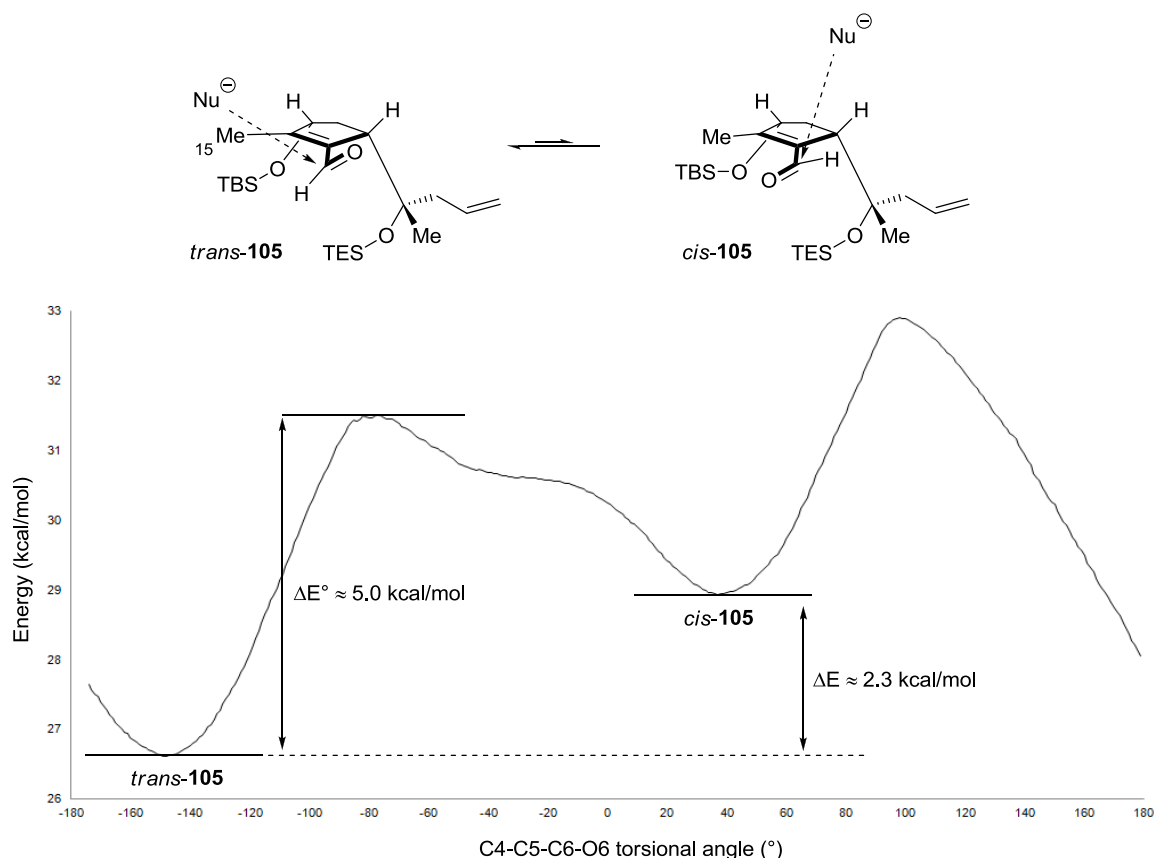


Figure 18. Rotational energy diagram of aldehyde **105**.

Because the product distribution does not mirror the expected equilibrium between the two conformations, the reaction can be assumed to be operating under the Curtin-Hammett principle, whereby the transition state leading to *cis*-**105** lies lower in energy to the transition state towards *trans*-**105**, leaving the reaction under kinetic control. A previous investigation of the reactivity differences between the conformation of acrolein has been performed by Houk *et al.* using *ab initio* MO calculations for the cyanide anion addition to the acrolein carbonyl, whereby the transition state of *cis* configured acrolein-addition is energetically favoured compared to the *trans* configuration (Figure 19), however there is no accounting for either the solvent system or the counter ion in this particular system.¹¹⁶ A small but important steric interaction with the C-15 methyl also seems likely, therefore further investigation of the relevant transition states is needed for a complete accounting of the stereocontrol exhibited.

¹¹⁶ Wong, S. S.; Paddon-Row, M. N.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 8679.

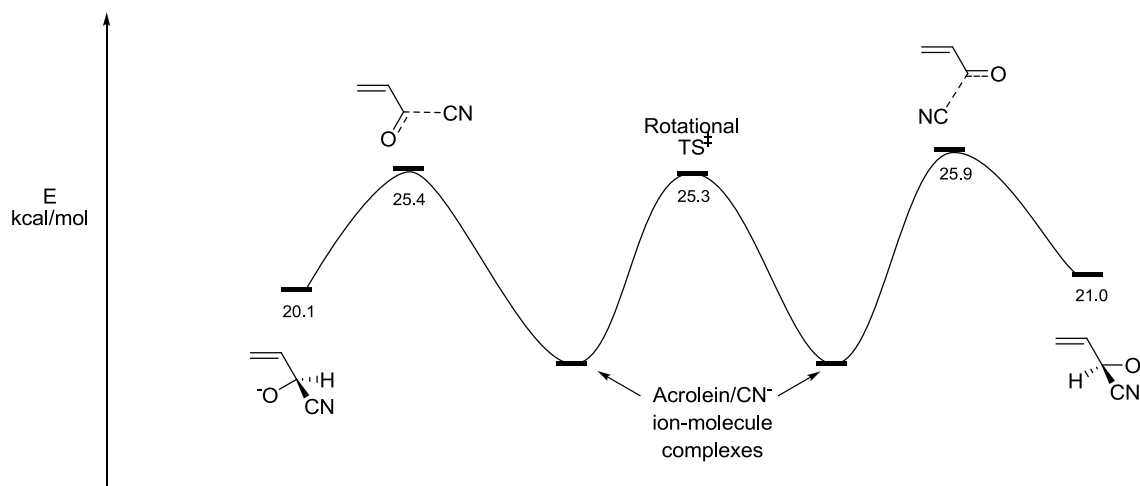


Figure 19. Energy diagram representation of *ab initio* MO calculations performed by Houk *et al.* on the addition of CN^- to acrolein.

Nevertheless, a range of alkynylation reactions were carried out with the previously observed near-complete stereocontrol (Table 5). The use of excess propiolate generally led to full consumption of the aldehyde starting material, and in general no reactivity difference was observed between 1.5 and 3.0 equivalents. A reduced reaction time to 1 hour also made little difference, as the alkynyl addition reaction generally seemed to be complete within 20 minutes according to monitoring *via* TLC. Various trapping reagents were used to generate the corresponding silyl ethers and acetyl esters. The assignment of the C-6 stereocentre was made based on previous results obtained by R. Bonepally with benzyl ester derivatives.¹¹⁷

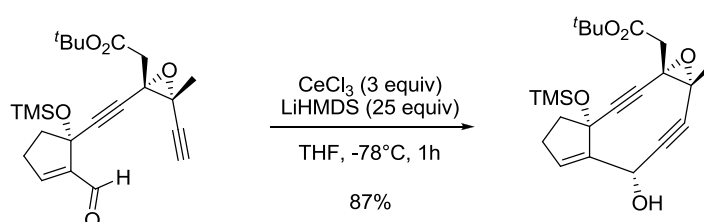
¹¹⁷ Jouanneau, M.; Bonepally, K. R.; Jeuken, A.; Tap, A.; Guillot, R.; Ardisson, J.; Férézou, J. P.; Prunet, J. *Org. Lett.* **2018**, *20*, 2176.

Table 5. Alkynylation of aldehyde **105**.

105

Entry	R ¹	R ²	Additive	Trapping agent	Product	Yield (%)
1	CO ² Me	H	CeCl ₃	H ₂ O	128	90
2	CO ₂ Me	TMS	None	TMSCl	129	100
3	CO ₂ Me	TMS	CeCl ₃	TMSCl	129	75
4	CO ₂ Me	Ac	None	AcCl	130	45
5	CO ₂ Me	Ac	None	Ac ₂ O	130	74
6	CO ₂ ^t Bu	H	CeCl ₃	H ₂ O	131	78
7	CO ₂ ^t Bu	TMS	None	TMSCl	132	32
8	CO ₂ ^t Bu	Ac	None	Ac ₂ O	133	80
9	CO ₂ Bn	H	CeCl ₃	H ₂ O	134	94

Dry cerium chloride¹¹³ additive was used to synthesise the corresponding α -alkynyl alcohols because the direct hydrolysis of the lithium alkynyl alkoxides failed to give reproducible yields. Reactivity towards hydrolysis of alkoxy cerium products can be expected to be lower compared to the lithium equivalents as cerium is less electropositive.¹¹⁸ This strategy was employed by Myers *et al.* during the total synthesis of neocarzinostatin (Scheme 60).¹¹⁹ An incomplete and less clean reaction was observed in the absence of CeCl₃.

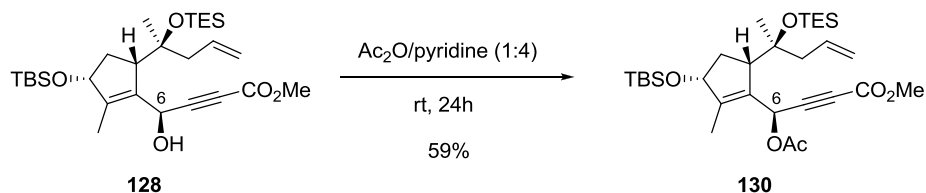
**Scheme 60.** Cerium(III) chloride mediated intramolecular alkynylation.

However, the use of cerium(III) chloride with a trapping agent other than H₂O led to a lower yield (Entry 3), presumably because the cerium alkoxide is less reactive. Acetylation was more efficient using acetic anhydride compared to acetyl chloride (Entries 4 and 5),

¹¹⁸ Athar, T.; Reddy, K. R. *Chinese J. Chem.* **2008**, *26*, 751.

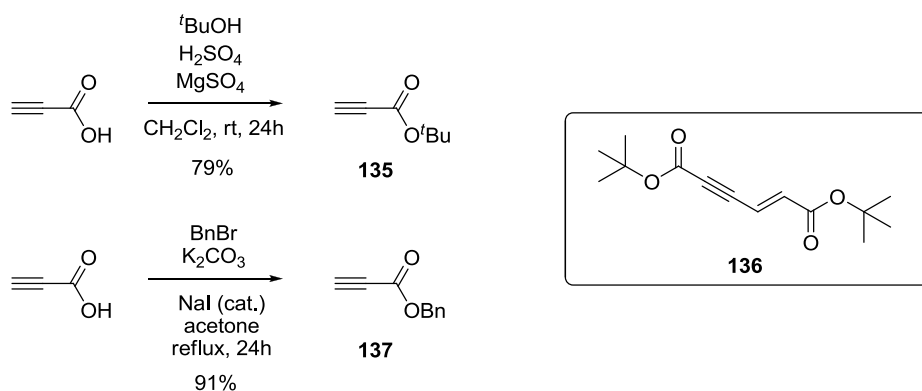
¹¹⁹ Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.

although sometimes small quantities of the original alcohol **128** can also be recovered. These could be converted to the C-6 acetylated product **130** by stirring in acetic anhydride/pyridine (Scheme 61).



Scheme 61. Propargylic alcohol acetylation.

The *tert*-butyl and benzyl ester equivalents could also be obtained (Entries 6-9) by the addition of the corresponding propiolate. *tert*-Butyl propiolate **135** was synthesised by several methods, most efficiently from propiolic acid and isobutene with sulfuric acid catalysis (Scheme 62), avoiding the commonly encountered base-catalysed byproduct **136**. Isobutene was generated *in situ* from *tert*-butyl alcohol.¹²⁰ Benzyl propiolate **137** was also prepared from propiolic acid by esterification with benzyl bromide.¹²¹



Scheme 62. Propiolic acid esterification.

¹²⁰ Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, 38, 7345.

¹²¹ Chalumeau, C.; Deffieux, D.; Chaignepain, S.; Quideau, S. *ChemBioChem* **2011**, 12, 1193.

3.3 Ring-closing ene-yne metathesis

3.3.1 RCEYM using Grubbs 2nd generation catalyst

Using previously reported conditions, the fully protected RCEYM substrates were converted into their respective bicyclic adducts without difficulty (Table 6).

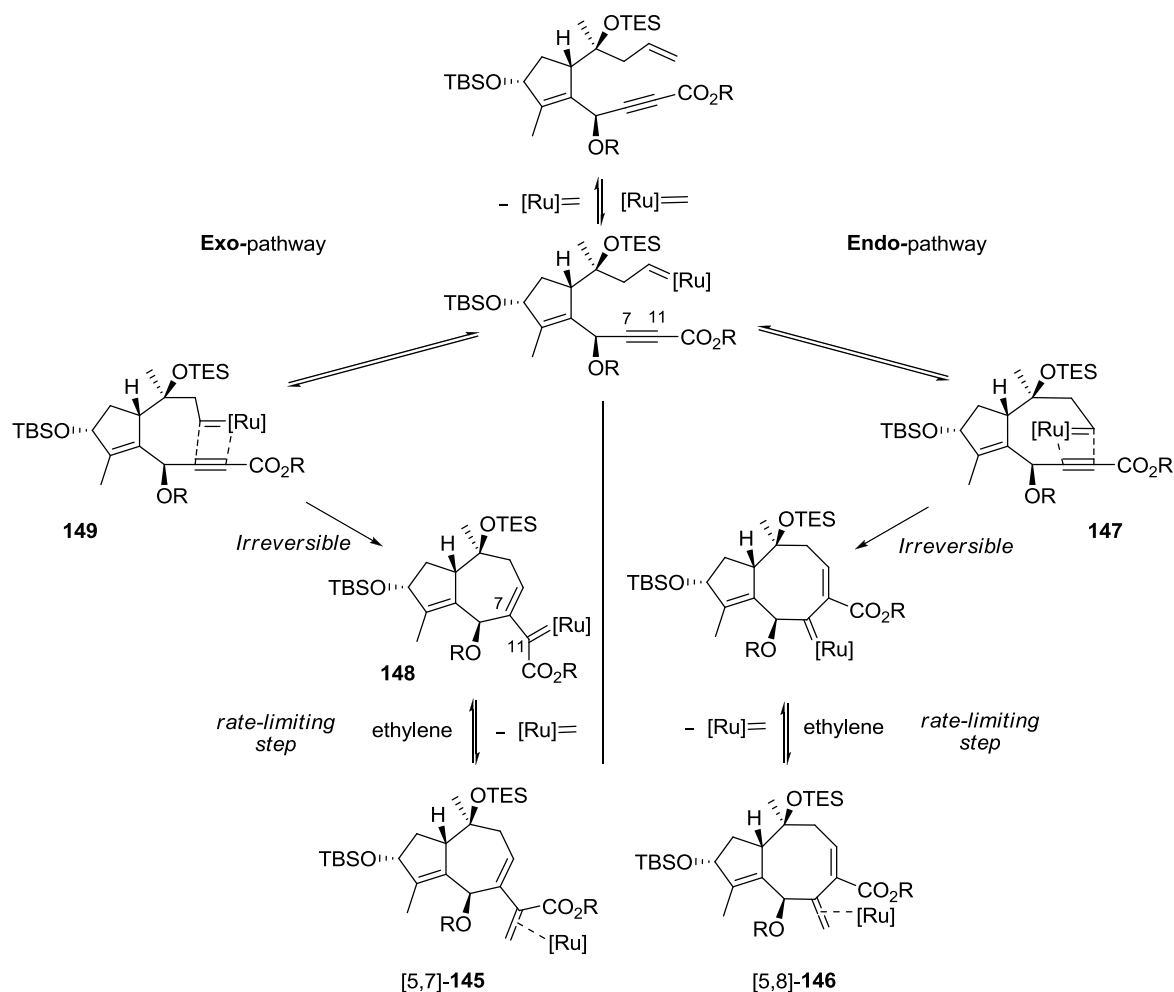
Table 6. Ring-closing ene-yne metathesis.

Entry	SM	R ¹	R ²	Temperature	108 (x mol%)	Product	Yield (%)
1	128	CO ² Me	H	80°C	20 mol%	138	63
2	129	CO ₂ Me	TMS	80°C	10 mol%	139	quant
3	130	CO ₂ Me	Ac	80°C	10 mol%	140	quant
4	131	CO ₂ ^t Bu	H	100°C	30 mol%	141	23
5	132	CO ₂ ^t Bu	TMS	80°C	10 mol%	142	76
6	133	CO ₂ ^t Bu	Ac	80°C	10 mol%	143	93
7	134	CO ₂ Bn	H	80°C	12.5 mol%	144	47

Grubbs-II **108**

Reactions of the free alkynyl alcohols **128**, **131** and **134** proceeded with difficulty, generally needing more catalyst to consume the starting material completely. *tert*-Butyl ester **131** required more forcing conditions, as the substrate only slowly degraded over time at 80°C (Entry 6). The proposed reaction pathways for the RCEYM reaction are shown in Scheme 63. The two pathways are based on DFT calculations performed on the entire ene-yne metathesis pathway by Straub *et al.*¹²²

¹²² Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444.



Scheme 63. Proposed RCEYM reaction pathway.

The important features to note are 1) the initial scission of the terminal alkene by the ruthenium alkylidene catalyst in accordance with the "ene-first" mechanistic pathway,¹²³ 2) no cyclobutene intermediate is thought to be present, 3) alkyne insertion into the ruthenium alkylidene is irreversible, 4) cycloreversion to product diene complexes **145** and **146** is the rate-limiting step in an ethylene atmosphere.

From here the apparent lower reactivity of free α -alkynyl alcohols can be partly rationalised. First, no [5,8] bicyclic products have been isolated or observed in these reactions, therefore the assumption can be made that the irreversible alkyne insertion step in the endo-pathway does not occur at significant rates and can therefore be excluded from the explanation. Extensive catalyst degradation during the reaction implies a

¹²³ Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762.

proportionately larger amount of unproductive metathetical reactions,¹²⁴ therefore either the energy barrier to alkyne insertion is increasing or the equilibrium lies more in the direction of intermediate **147**. Since the rate-limiting step is thought to be the cycloreversion of ruthenium carbene **148** it is likely that the latter is contributing to the rate reduction. Increased steric bulk ($\text{Me} < \text{Bn} < \text{tBu}$) of the various propiolic esters is correlated to decreasing reactivity, likely because steric interactions between the bulky spectating ligands and the ester moieties disfavour approach of the ruthenium alkylidene in conformation **149**. This has been noticed before during the ene-yne CM of alkynes with significant steric difference between the two alkyne sites.¹²⁵ Finally, propargylic alcohols can not only coordinate to ruthenium and favour the endo-conformation **147**, but also interfere with the rate-determining cycloreversion process by stabilising ruthenium carbene in complex **150**, which stabilises the proposed catalytic resting state **151** after alkyne insertion (Figure 20), thereby retarding the regeneration of active catalyst. Protection of the hydroxyl group not only prevents this coordination but also can be expected to enhance the RCEYM through the Thorpe-Ingold effect in combination with bulky trimethylsilyl ethers.¹²⁶

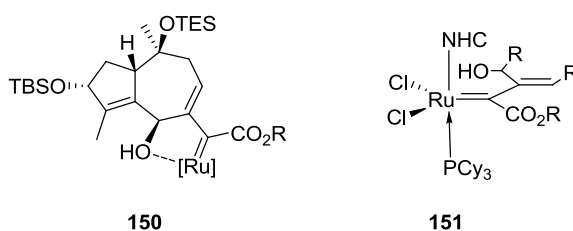


Figure 20. Propargyl alcohol coordinative stabilisation of a ruthenium carbene and the proposed catalyst resting state.

Similar inhibition of enyne metathesis by nearby electron-donation capable heteroatoms has been noticed before. During the total synthesis of several epoxyquinoids, propargyl alcohol **152** did not proceed to the desired REYCM-metallotropically shifted product **153** (Scheme 64).¹²⁷ Although reaction failure was attributed to steric congestion around the vinyl group, heteroatom coordination of the methoxymethyl group (**154**) or indeed the free hydroxyl (**155**) is possible, thereby preventing the reaction from proceeding. By changing

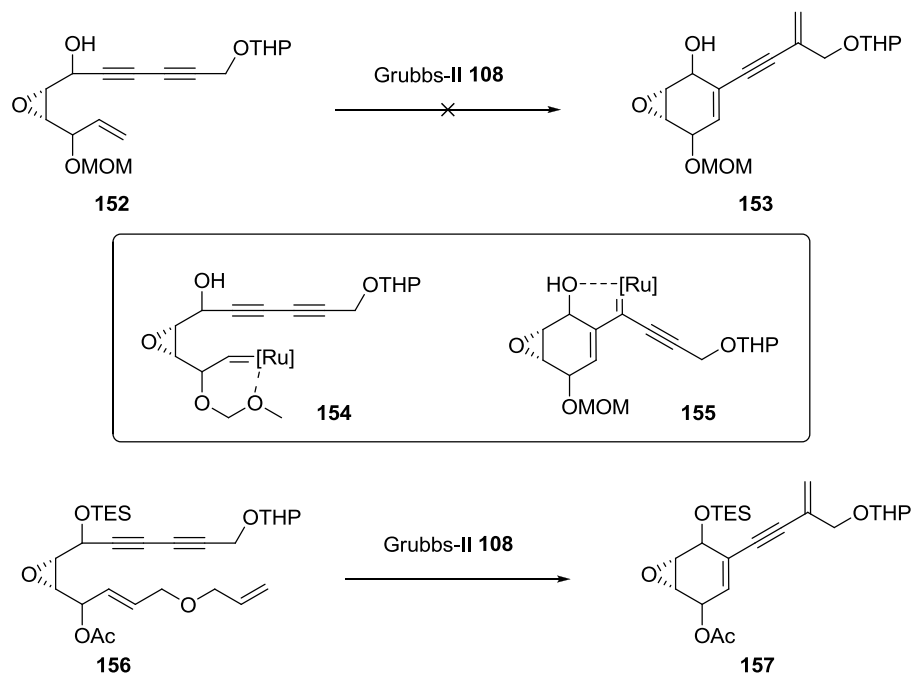
¹²⁴ Engel, J.; Smit, W.; Foscatto, M.; Occhipinti, G.; Törnroos, K. W.; Jensen, V. R. *J. Am. Chem. Soc.* **2017**, *139*, 16609.

¹²⁵ Le-Ravalec, V.; Dupé, A.; Fischmeister, C.; Bruneau, C. *ChemSusChem* **2010**, *3*, 1291.

¹²⁶ Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267.

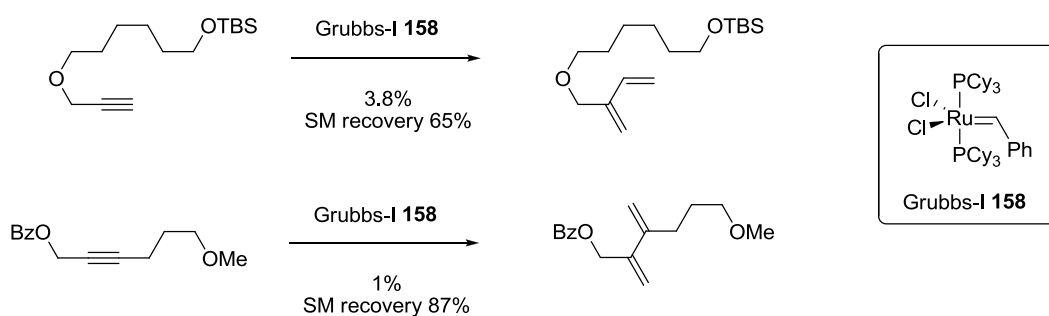
¹²⁷ Li, J.; Park, S.; Miller, R. L.; Lee, D. *Org. Lett.* **2009**, *11*, 571.

the protection strategy in propargyl silyl ether **156** and introducing a relay-metathesis strategy, the desired transformation to adduct **157** was possible.



Scheme 64. Heteroatom hindrance of a RCEYM strategy towards epoxyquinoids.

Mori also noticed a near-complete reduction in activity during cross ene-yne metathesis (CEYM) of various substrates bearing heteroatoms catalysed by **158**; mostly starting materials were recovered from these reactions (Scheme 65).¹²⁸



Scheme 65. Heteroatom interference in CYEM.

¹²⁸ Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, 55, 8155.

3.3.2 Further exploration of RCEYM conditions

Varying the ligand substitution around ruthenium metathesis catalysts can have many dramatic effects on their reactivity patterns. Because the bicyclic alcohol adducts **138**, **141** and **144** seemed to offer a promising way forward with the synthesis, other RCEYM conditions were explored in an attempt to overcome the previously lacklustre reactions. Hoveyda-Grubbs 2nd-generation catalyst **159** and derivatives offer enhanced thermal stability compared with phosphine-containing analogues;¹²⁹ M71-SIMes **160** bears an additional trifluoromethylamide substituent on the isopropoxystyrenyl carbene, the electron-withdrawing effect of which allows it to initiate the reaction faster compared to its parent catalyst **159**.¹³⁰ As well as tuning electronic properties, steric interactions on the N-heterocyclic carbene (NHC) ligands can be varied to good effect; M20-SIPr **161** bears bulky isopropyl groups,¹³¹ whereas the Stewart-Grubbs catalyst **162** has a decreased steric interaction compared to its parent Grubbs-II catalyst **108** owing to the mono-substituted ortho-methyl tolyl NHC.¹³² These complexes have all been documented to catalyse various RCEYM and CEYM reactions (Scheme 66).^{133,134}

¹²⁹ Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

¹³⁰ Clavier, H.; Caijo, F.; Borré, E.; Rix, D.; Boeda, F.; Nolan, S. P.; Mauduit, M. *European J. Org. Chem.* **2009**, *25*, 4254.

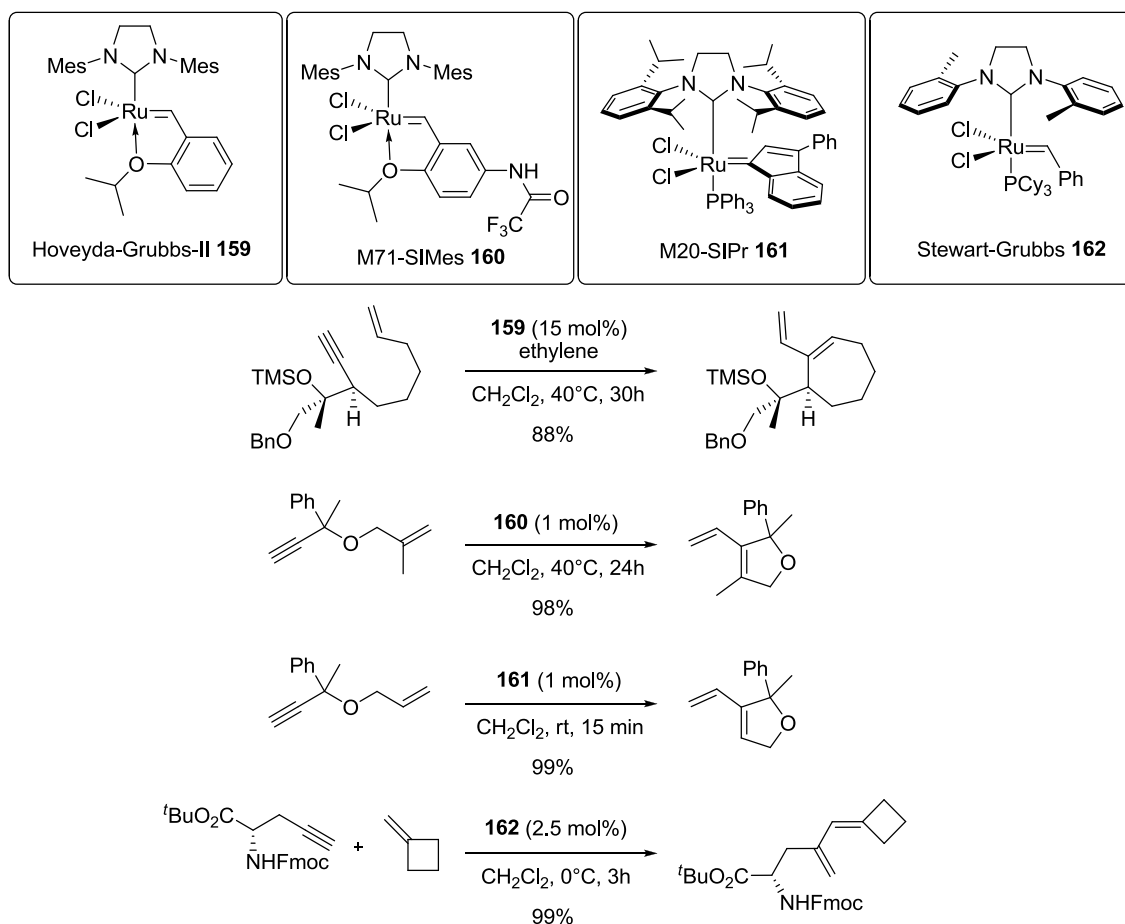
¹³¹ Urbina-Blanco, C. A.; Manzini, S.; Gomes, J. P.; Doppiu, A.; Nolan, S. P. *Chem. Commun.* **2011**, *47*, 5022.

¹³² a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.

b) Laroche, B.; Detraz, M.; Blond, A.; Dubost, L.; Mailliet, P.; Nay, B. *J. Org. Chem.* **2015**, *80*, 5359.

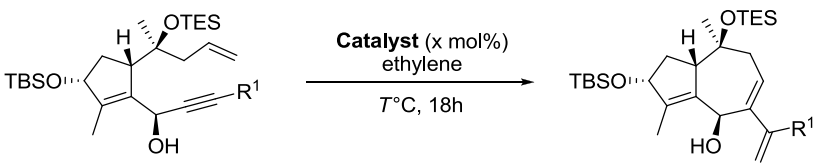
¹³³ Paquette, L. A.; Kwong, W. L. *Org. Lett.* **2008**, *10*, 2111.

¹³⁴ Clark, D. A.; Basile, B. S.; Karnofel, W. S.; Diver, S. T. *Org. Lett.* **2008**, *10*, 4927.



Scheme 66. Catalyst variety in RCEYM and CEYM reactions.

Table 7 summarises the new RCEYM conditions attempted on various propargylic alcohols. Catalysts **160** and **161** were provided by Umicore N.V. and gratefully received.

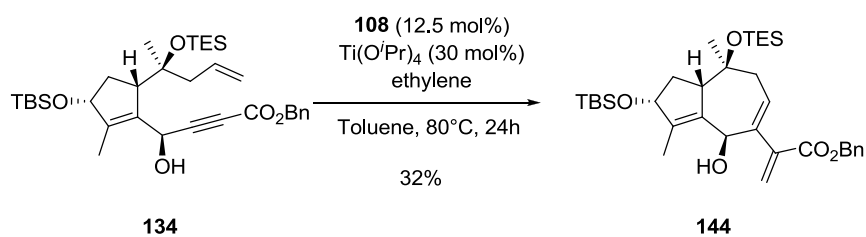
Table 7. New conditions for RCEYM.


Entry	SM	R ¹	Catalyst	Temperature	Time	Yield (%)
1 ^a	128	CO ₂ Me	159 (10 mol%)	80°C	18h	n.r.
2 ^b	134	CO ₂ Bn	160 (2 mol%)	40°C	18h	n.r.
3 ^c	134	CO ₂ Bn	160 (2 mol%)	80°C	24h	n.r.
4 ^a	134	CO ₂ Bn	161 (2 mol%)	80°C	24h	n.r.
5 ^b	134	CO ₂ Bn	162 (2 mol%)	40°C	18h	n.r.
6 ^a	134	CO ₂ Bn	162 (2 mol%)	80°C	18h	n.r.
7 ^a	134	CO ₂ Bn	162 (10 mol%)	80°C	24h	^d

a) Reaction performed in toluene [0.02 M]. b) Reaction performed in CH₂Cl₂ [0.02 M]. c) Reaction performed in DCE [0.02 M]. d) extensive degradation of starting material.

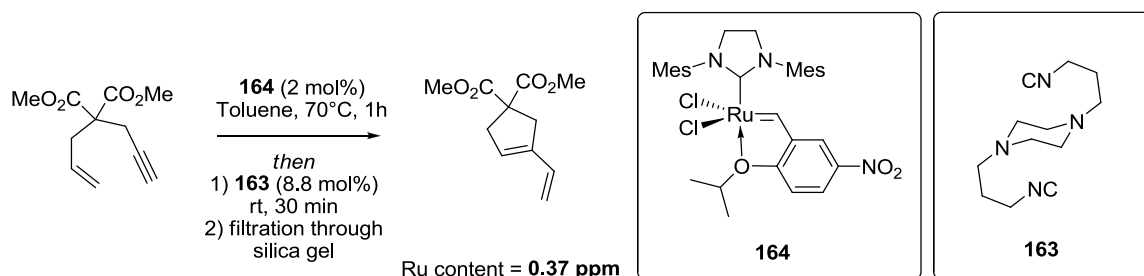
Disappointingly none of the conditions produced even traces of product; they mostly led to recovery of a reduced amount of starting material after column chromatography. The failure of the Grubbs-II type **162** to catalyse any RCEYM reactions was particularly puzzling.

The use of Lewis acids to complex with polar heteroatom groups that interfere in metathesis has been used to great effect by Percy *et al.* in the synthesis of allylic alcohol-containing eight-membered rings.¹³⁵ However, when this approach was applied to our substrate no improvement was noticed, in fact the reaction proceeded more sluggishly than before, and only 32% of desired bicyclic adduct **144** was obtained (Scheme 67).

**Scheme 67.** Attempted RCEYM enhancement through the use of a Lewis acid.

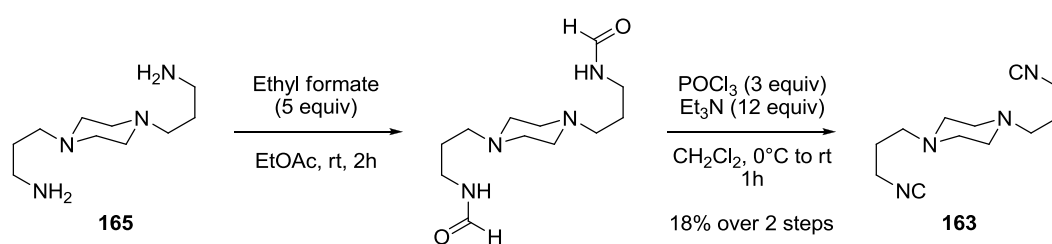
¹³⁵ Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2008**, *73*, 2389.

Finally, it was noticed that many bicyclic adducts contained the characteristic yellow/brown colour from [Ru] contamination, especially at the higher catalysts loadings required for propargylic alcohol substrates, even after several chromatographic purifications. All adducts were prone to degradation under ambient conditions over the course of several days to a week, therefore it might be desirable to remove as much [Ru] as possible, metathetically active or not, after the reaction has been stopped.



Scheme 68. Example isocyanide-quenched RCEYM reaction.

Grela has shown that isocyanide ruthenium scavenger **163** has a remarkable ability to remove residual [Ru] from reactions with **164** after filtration through a short silica plug (Scheme 68).¹³⁶ The easily handled crystalline solid was prepared in two steps from *bis*-piperazine derivative **165** (Scheme 69), but unfortunately its inclusion in previous metathesis reactions did not lead to an overall improvement in either isolated yield or product stability.

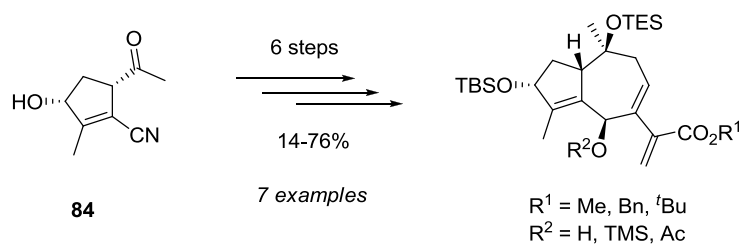


Scheme 69. Synthesis of isocyanide scavenger.

¹³⁶ Szczepaniak, G.; Urbaniak, K.; Wierzbicka, C.; Kosiński, K.; Skowerski, K.; Grela, K. *ChemSusChem* **2015**, 8, 4139.x

3.4 Conclusions

A wide range of [5,7]-bicyclic structures **138-144** have been synthesised through the use of improved allylation and alkynylation procedures, followed by the application of the key ring-closing ene-yne metathesis step (Scheme 70).

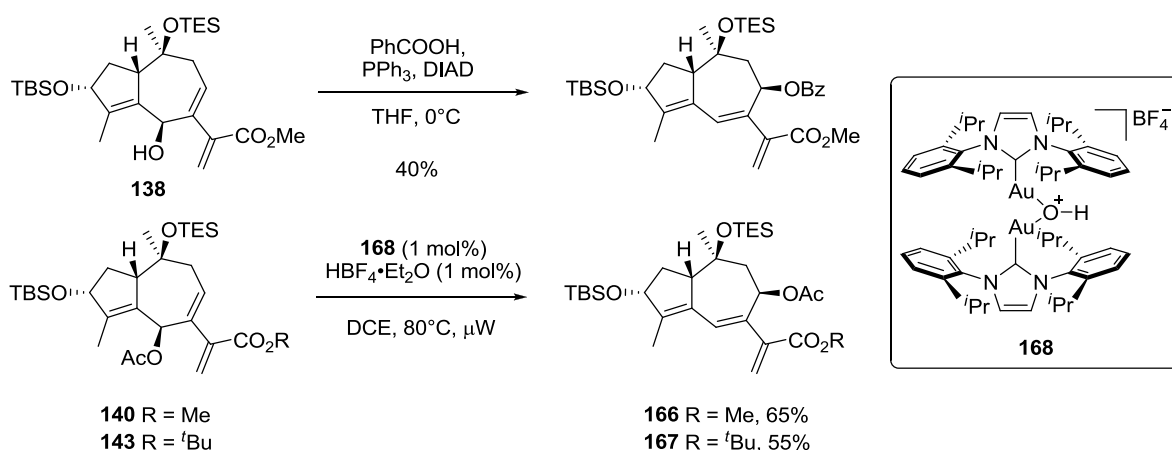


Scheme 70. Summary of route towards [5,7]-bicycles from ketone **84**.

Chapter 4: Derivatisation of [5,7]-bicyclic structures

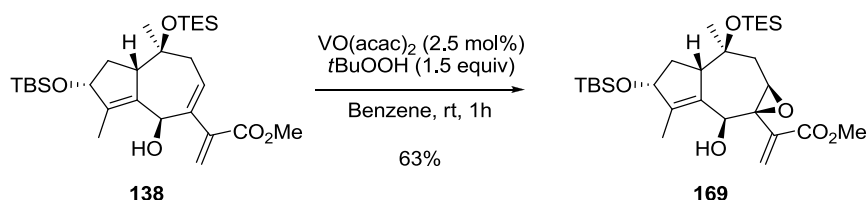
4.1 Previous derivatisation attempts by F  r  zou *et al.*

Several attempts were made to derivatise some of the bicycles previously obtained by F  r  zou *et al.* Degradation is a common outcome under more forcing conditions because these substrates have proven to be rather sensitive. However, an S_N2' reaction under Mitsunobu conditions was observed for allylic alcohol **138**, and the rearrangement of allylic acetates **140** and **143** using Au(I)-catalysis¹³⁷ proceeded to give the C-8 acetate adducts **166** and **167** (Scheme 71) using complex **168**.



Scheme 71. Previously successful derivatisation of [5,7]-bicycles.

Further preliminary investigations conducted by R. Bonnelly showed that selective directed epoxidation onto the C-7/8 double bond could be achieved (Scheme 72).



Scheme 72. Directed epoxidation.

¹³⁷ a) G  mez-Su  rez, A.; Oonishi, Y.; Meiries, S.; Nolan, S. P. *Organometallics* **2013**, 32, 1106.

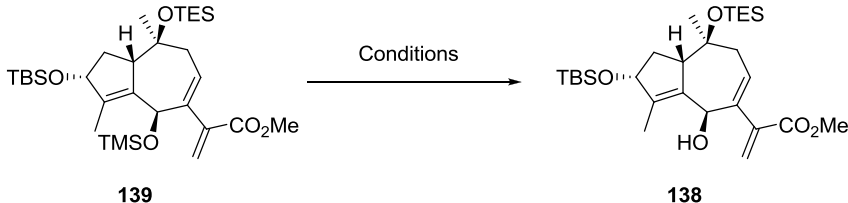
b) Gaillard, S.; Bosson, J.; Ram  n, R. S.; Nun, P.; Slawin, A. M. Z.; Nolan, S. P. *Chem. - A Eur. J.* **2010**, 16, 13729.

4.2 Selective deprotection of persilylated compounds

Because RCEYM reactions of propargylic alcohols were not always efficient compared to those of their protected analogues, the use of selective deprotection of the latter was one way to attempt to obtain reliable quantities of allylic alcohols **138**, **142** and **144**. Additionally, there was a marked increase in stability of fully silylated substrate **138** compared to other adducts derived from starting nitrile **104**; it showed no sign of decomposition in ambient conditions over the course of several weeks.

Table 8 lists a range of deprotection conditions that were explored. In addition, use of TBAF was previously shown to affect global deprotection. Only acid-mediated deprotections provided any selectivity (Entries 2, 8, and 11) but in general these reactions were not reproducible.

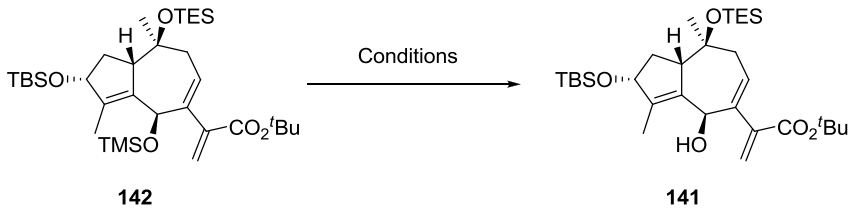
Table 8. Selective deprotection of persilylated **139**.

				
Entry	Conditions	Time	Temp (°C)	Yield (%)
1	HF-Pyridine, THF/Pyridine (10:1)	4h	rt	n.r.
2	PPTS (6 mol%) MeOH/CH ₂ Cl ₂ (1:1)	1h	rt	34
3	AcOH, H ₂ O, THF (4:1:1)	1h	rt	degradation
4	KF, TEG	24h	rt	n.r.
		24h	50	degradation
5	Sc(OTf) ₃ (0.5 mol%), H ₂ O (5 equiv), THF	10 min	-20	degradation
6	FeCl ₃ (1 mol%), CH ₃ CN	10 min	-20	degradation
7	I ₂ (5 mol%), MeOH	10 min	rt	degradation
8	I ₂ (5 mol%), MeOH	3.5h	-78	73 ^a
9	K ₂ CO ₃ , MeOH	72h	rt	n.r.
10	MeOH, sonication	3 min	rt	^b
11	citric acid (10 mol%), MeOH	4h	rt	22 ^a
12	0.1N HCl, THF	24h	rt	n.r.

a) Not reproducible. b) Mixture of deprotected products.

Similarly, deprotection of silylated *tert*-butyl ester **142** also does not exhibit a high degree of selectivity (Table 9). A small range of deprotection conditions was tested on this substrate but none of the reactions showed any level of effective deprotection, but instead resulted in extensive degradation. In contrast to methyl ester **138**, storage of **142** under air resulted in some desilylation, along with recovery of starting material and marked degradation. Therefore this route to C-6 alcohols was not pursued further.

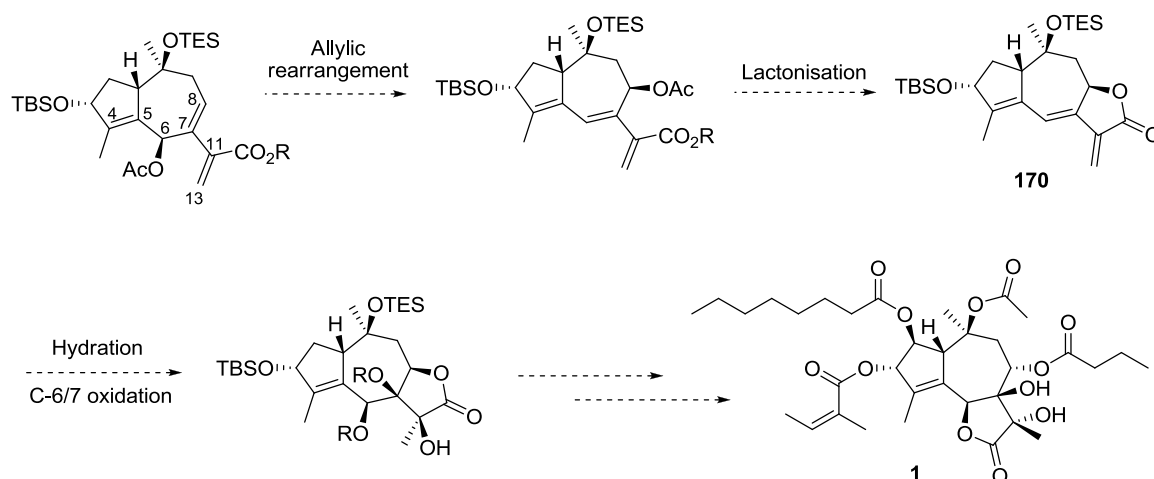
Table 9. Selective deprotection of persilylated **142**.

				
Entry	Conditions	Time	Temp (°C)	Yield (%)
1	5% HF/MeCN	30 min	-42 to -20	degradation
2	K ₂ CO ₃ , MeOH	1h	rt	degradation
3	citric acid (10 mol%), MeOH	1h	rt	degradation
4	Ambient storage	14d	rt	23 ^b

a) 45% recovery of SM.

4.3 Allylic acetate rearrangement

According to previous results (Scheme 71), allylic acetates **140** and **143** could undergo rearrangement to adducts **166** and **167** respectively. This led to the synthetic strategy outlined in Scheme 73, whereby hydration across the acrylate olefin and oxidation of the C-6/7 olefin of **170** could be facially controlled, based on previous conformational analysis.



Scheme 73. Synthetic strategy from acetates **140** and **143** to thapsigargin **1**.

The C-8 acetate rearranged product **166** is expected to be thermodynamically favoured due to increased π -bond conjugation,¹³⁸ indeed some rearrangement was noticed during prolonged contact with silica gel during chromatographic purification of the preceding metathesis reaction, and this has been noted before during the synthesis of analogous allylic acetates.¹³⁹ By stirring **140** in a slurry of silica gel, the rearranged acetate **166** could be isolated *via* preparative thin layer chromatography upon complete consumption of starting material, alongside numerous other unidentified rearrangement and decomposition products in complex mixtures (Scheme 74).



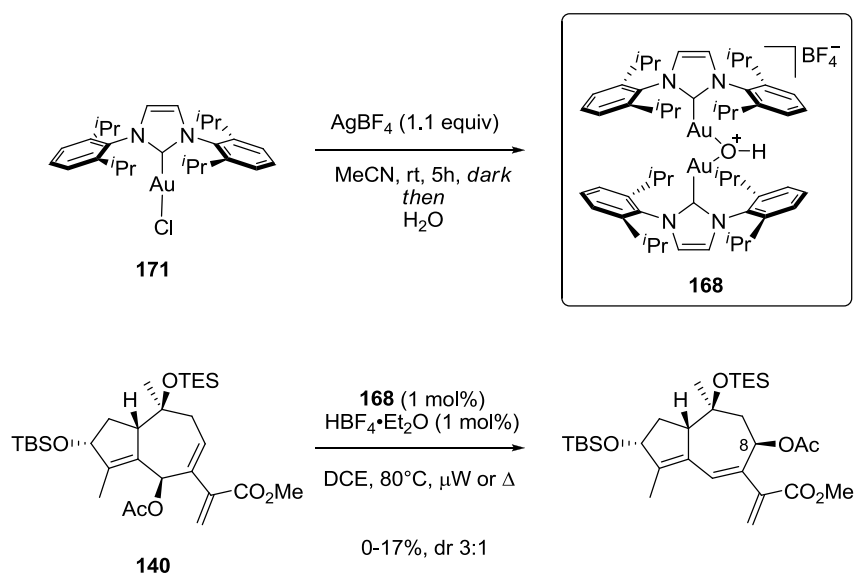
Scheme 74. SiO₂-mediated allylic rearrangement.

When Nolan's silver-free (NHC)-Au(I) pre-catalyst **168**, synthesised from commercially available (IPr)AuCl **171**,¹³⁷ was used, the previously reported outcomes could unfortunately not be reproduced (Scheme 75). Under both microwave and conventional heating, substrate **140** produced a complex mixture of products from which adduct **166** could be isolated in poor yield and surprisingly as a mixture of C-8 diastereomers (dr 3:1). The proposed [3,3]-sigmatropic rearrangement reaction mechanism for Au(I)-catalysed

¹³⁸ Oehlschlager, C.; Mishra, P.; Dharmi, S. *Can. J. Chem.* **1984**, 62, 791.

¹³⁹ Serra-Muns, A.; Guérinot, A.; Reymond, S.; Cossy, J. *Chem. Commun.* **2010**, 46, 4178.

allylic acetate rearrangement should proceed with transfer of stereochemical information between the starting and product allylic sites,¹⁴⁰ so isolation of an isomeric mixture indicates a possible competing general acid catalysed reaction pathway under the reaction conditions.



Scheme 75. Rearrangement under Nolan's silver-free conditions.

A further small screening of earlier conditions employed by Nolan *et al.*¹⁴¹ also produced disappointing yields and diastereomeric mixtures (Table 10). The *tert*-butyl ester **143** reacted to give only complex mixtures and the product could not be isolated.

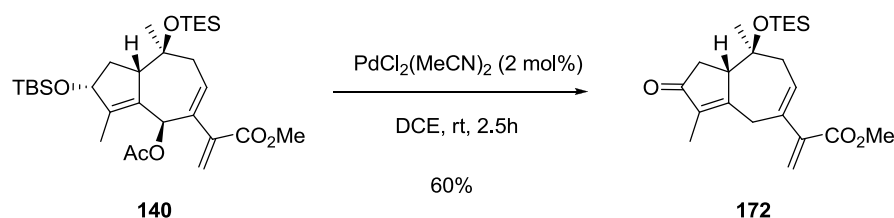
¹⁴⁰ a) Freindorf, M.; Cremer, D.; Kraka, E. *Mol. Phys.* **2018**, *116*, 611. b) Gourlaouen, C.; Marion, N.; Nolan, S. P.; Maseras, F. *Org. Lett.* **2009**, *11*, 81.

¹⁴¹ Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653.

Table 10. Screening of allylic acetate rearrangement conditions.

Entry	Substrate	Additive	Time	Temp (°C)	Product	Yield (%)
1	140	AgOTf (2 mol%)	1h	80, μ W	166	degradation
2	140	AgBF ₄ (2 mol%)	30 min	80, μ W	166	28 (dr 3:1)
3	140	AgBF ₄ (2 mol%)	30 min	80	166	degradation
4	143	AgBF ₄ (2 mol%)	30 min	80, μ W	167	complex mixture
5	143	AgBF ₄ (2 mol%)	30 min	80	167	complex mixture

Overman's Pd(II) allylic ester rearrangement¹⁴² of adduct **140** resulted only in product **172** (Scheme 76), the mechanism of which will be explored later. A similar apparent [1,4]-hydride shift/elimination has been reported before under Pd(II) catalysis during the synthesis of (–)-shikimic acid.¹⁴³

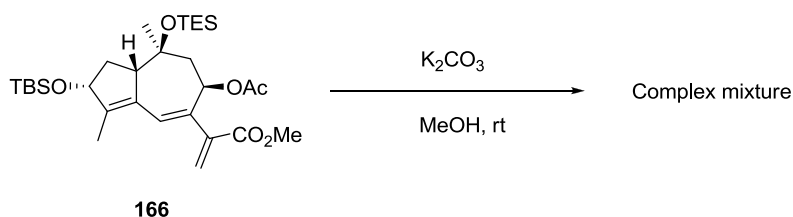
**Scheme 76.** Rearrangement under Overman conditions.

Attempts to lactonise acetate **166** under standard conditions also met with failure and produced complex mixtures (Scheme 77).

¹⁴² a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 20, 321.

b) Golding, B. T.; Pierpoint, C.; Aneja, R. *J. Chem. Soc. Chem. Commun.* **1981**, 1030.

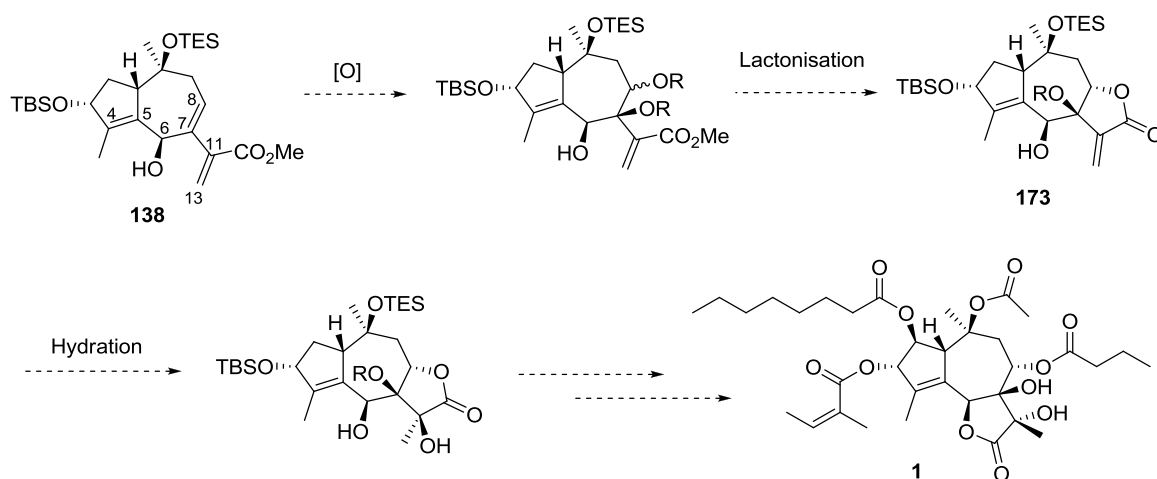
¹⁴³ Yoshida, N.; Ogasawara, K. *Org. Lett.* **2000**, 2, 1461.



Scheme 77. Attempted lactonisation of rearranged acetate **166**.

4.4 Chemoselective oxidation of the C-7/8 alkene

All of the bicycles that had been made so far contain three alkene functional group sites, which are differentiated by their substitution patterns and electronic properties. The C-11/13 olefin is considerably electron-deficient, while the C-4/5 olefin is electron-rich but also tetrasubstituted, differentiating it from the C-7/8 double bond. The C-6 alcohol is allylic to both of these alkenes and so the correct oxidative conditions are critical to the selective oxidation the C-7/8 alkene. Scheme 78 shows the new proposed strategy towards the fully oxygenated thapsigargin core. First, oxidation of the C-7/8 olefin can fix the pendent C-11/13 olefin into an orientation that favours hydration across the correct face of lactone **173**, which can then be taken on to thapsigargin **1**.

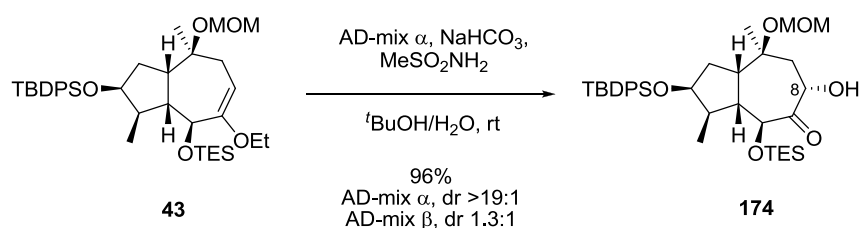


Scheme 78. Proposed oxidation strategy towards thapsigargin **1**.

4.4.1 Chemoselective dihydroxylation

4.4.1.1 Osmium(VIII) dihydroxylation

The catalytic use of osmium tetroxide for the dihydroxylation of alkenes is prolific in natural product synthesis, as the vicinal-diol motif is a common building block for many classes of compounds, including sesquiterpenes.¹⁴⁴ All three previous total syntheses of thapsigargin have included the use of either Sharpless asymmetric dihydroxylation or catalytic Upjohn dihydroxylation in order to access the highly oxidised core structure. Ley's approach to ketone **174** included the use of commercial AD-mix α to access the crucial C-8 stereochemistry (Scheme 79), while it was noted that AD-mix β resulted in a mixture of products.



Scheme 79. Dihydroxylation during Ley's total synthesis of thapsigargin.

Bulky non-acidic allylic stereocentres generally direct dihydroxylation towards the opposite face, as is the case with substrate **43**. However, wider substrate control can also control the dihydroxylation stereochemistry; during the total synthesis of Gabosine J, Figueredo *et al.* obtained a mixture of diols **175/176** from silyl ether **177**.¹⁴⁵ The influence of the pseudoaxial thioether partially directed the osmylation to the opposite face, despite the influence of the preconfigured allylic TBS ether (Figure 21). Based upon these results, it was surmised that **139** could undergo at least partial dihydroxylation on the β -face in order to install the correct stereochemistry of the C-7 tertiary alcohol (Figure 21), as the allylic TMS ether is predicted to lie pseudoequatorially in order to minimise transannular strain, alleviating some of the steric hindrance of the β -face.

¹⁴⁴ Heravi, M. M.; Zadsirjan, V.; Esfandyari, M.; Lashaki, T. B. *Tetrahedron: Asymmetry* **2017**, 28, 987.

¹⁴⁵ Fresneda, M. Á.; Alibés, R.; Font, J.; Bayón, P.; Figueredo, M. *J. Org. Chem.* **2012**, 77, 5030.

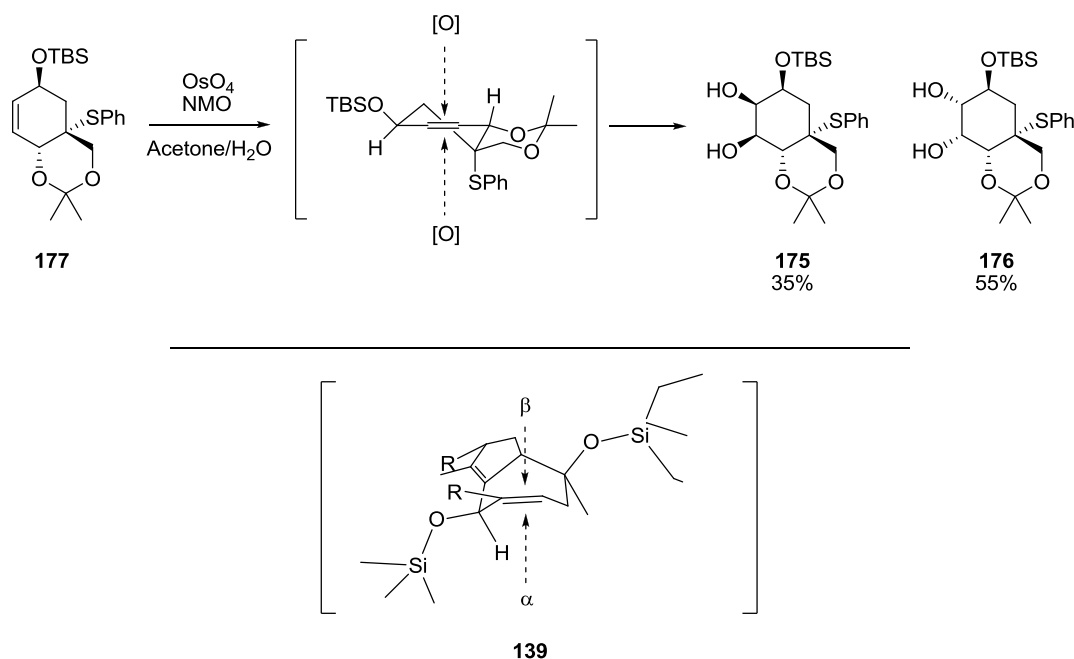
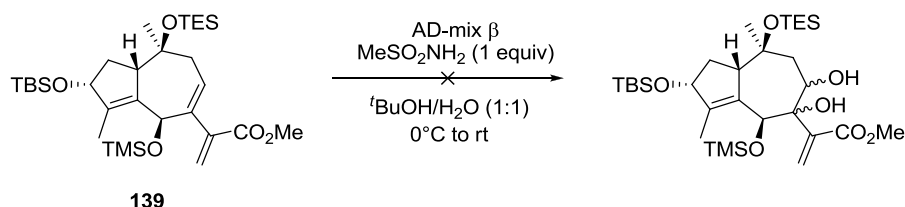


Figure 21. Dihydroxylation during the synthesis of Gabisone J and proposed configuration of silyl ether **139**.

Unfortunately, subjecting silyl ether **139** to Sharpless asymmetric dihydroxylation conditions promoted by methylsulfonamide¹⁴⁶ did not result in any detectable conversion, giving only recovered starting material (Scheme 80).



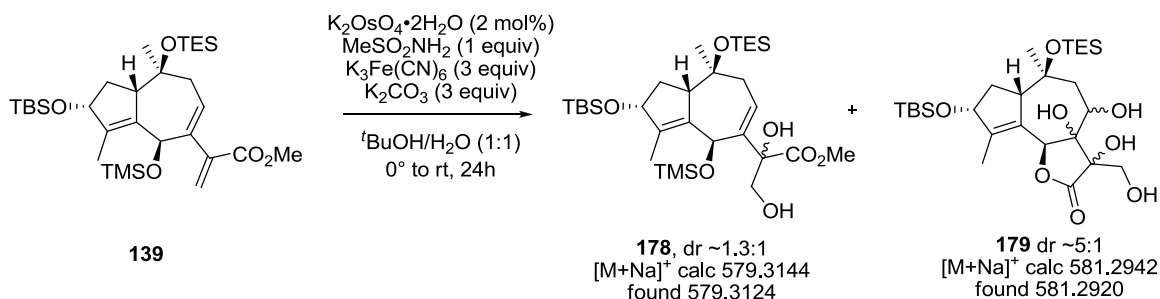
Scheme 80. Attempted dihydroxylation using AD-mix α .

Under more forcing conditions, a higher loading of osmium precatalyst $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (2 mol%) was added under Sharpless biphasic conditions.¹⁴⁷ This led to a complex mixture of products (Scheme 81), as well as recovery of most of the starting material. These products were difficult to isolate due to separation issues and low quantities, but crude NMR analysis combined with mass spectrometry pointed to the formation of a diastomeric

¹⁴⁶ Junttila, M. H.; Hormi, O. O. E. *J. Org. Chem.* **2009**, *74*, 3038.

¹⁴⁷ Hoi-Lun, K.; Sorato, C.; Ogino, Y.; Hou, C.; Sharpless, B. K. *Tetrahedron Lett.* **1990**, *31*, 2999.

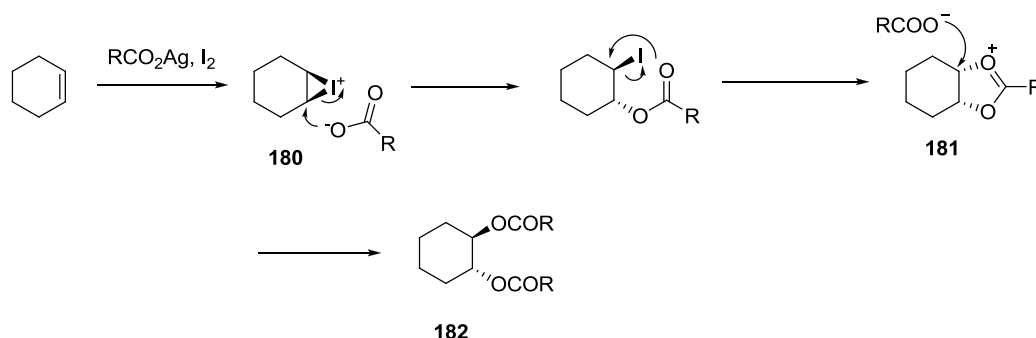
mixture of diol **178**, as well as the concurrent deprotection of the TMS-ether and dihydroxylation/lactonisation to give tetrol **179**.



Scheme 81. Osmylation under Sharpless biphasic conditions.

4.4.1.2 Prévost reaction

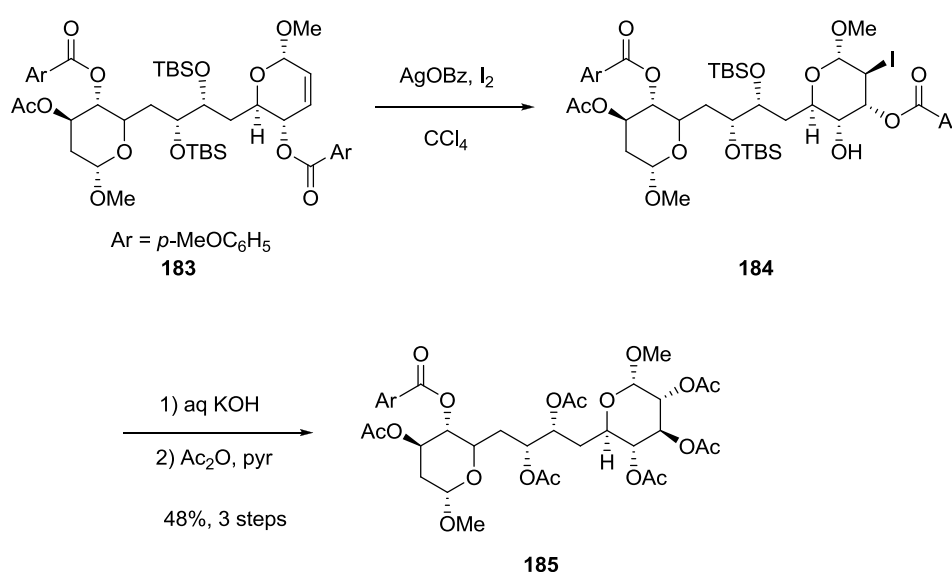
The Prévost reaction and the related Woodward reaction (or modification) also allows for the synthesis of vicinal diols, in an *anti* and *cis* selective manner, respectively. The classical Prévost reaction conditions involve the stoichiometric use of a silver carboxylate and molecular iodine. The reaction operates by the initial formation of RCOOI , which forms a transient cyclic iodonium ion **180** on the target alkene (Scheme 82). This intermediate can be trapped by internal or external nucleophiles. Anchimeric assistance then liberates iodide by forming oxonium **181**. This can be trapped once more by a nucleophile to generate the *anti*-configured product **182**. The addition of water to this reaction decomposes the intermediate oxonium **181** directly to the *syn*-substituted product and this is called the Woodward modification.¹⁴⁸



Scheme 82. Model Prévost reaction scheme.

¹⁴⁸ Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.

Although not as popular as other dihydroxylation methods due to the use of large amounts of silver carboxylates and molecular halides, the method has found a continuing use in total synthesis. During the synthesis of the C-58/71 fragment of palytoxin, Nelson *et al.* took advantage of an interrupted Prévost reaction of substrate **183** when the intermediate iodonium was trapped by a neighbouring *para*-methoxybenzoate to an oxonium ion which is apparently stable under the reaction conditions, yielding *syn*-hydroxy *p*-methoxybenzoate **184** as the major product upon aqueous workup (Scheme 83).¹⁴⁹ This iodide could be converted into the 1,2-*anti*-heptaacetate palytoxin C-58/C-71 fragment **185**.



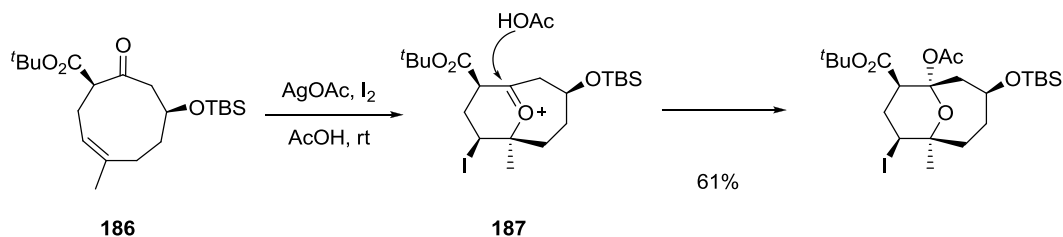
Scheme 83. Interrupted Prévost reaction during the synthesis of the C-58/71 fragment of palytoxin.

Clarke *et al.* used the Prévost reaction conditions to affect a transannular cyclisation of ketone precursor **186** during synthetic studies towards the D,E,F rings of FR182877 and hexacyclinic acid (Scheme 84).¹⁵⁰ The cyclisation reaction was rationalised by the quenching of intermediate oxonium ion **187** by the acetic acid solvent.

¹⁴⁹ a) Hodgson, R.; Nelson, A. *Org. Biomol. Chem.* **2004**, 2, 373.

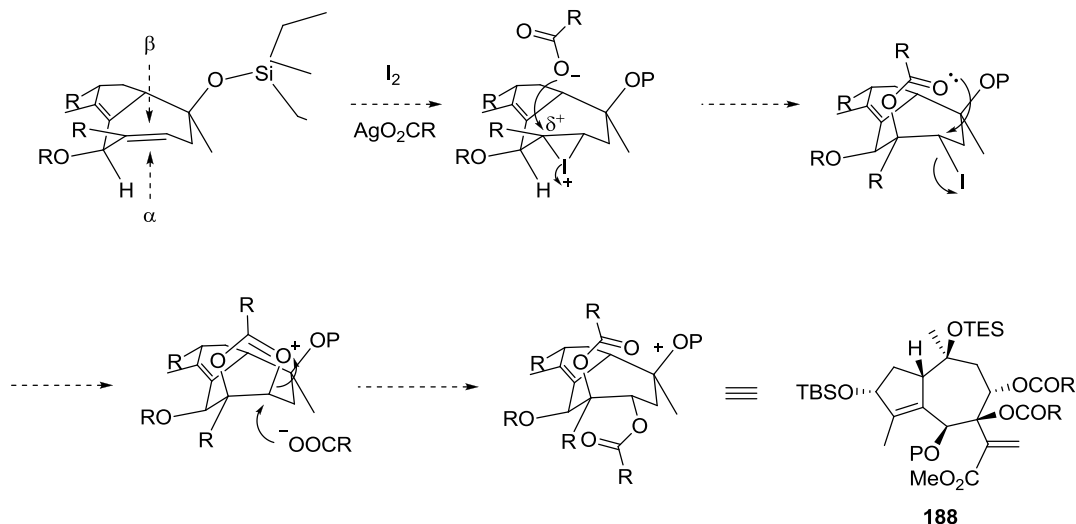
b) Hodgson, R.; Mahid, T.; Nelson, A. *Chem. Commun.* **2001**, 1, 2076.

¹⁵⁰ Clarke, P. A.; Grist, M.; Ebdon, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, 61, 353.



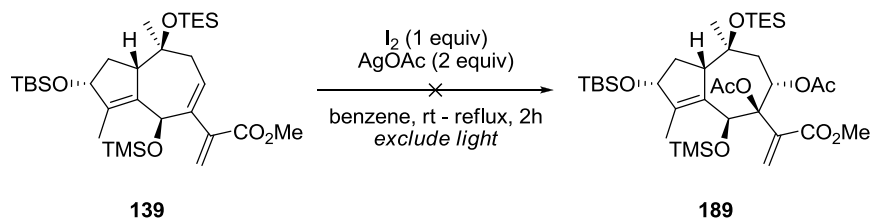
Scheme 84. Transannular cyclisation under Prévost conditions.

The double inversion approach of the Prévost reaction is well suited to the more readily accessible α -face of bicyclic substrates **138-144**. As the iodonium intermediate forms on the α -face, initial nucleophilic attack is expected to occur on the C-7 position as the partial positive charge is stabilised by the adjacent vinyl group (Scheme 85). Neighbouring group assistance then provides the desired 1,2 *anti*-configured vicinal diester **188**.



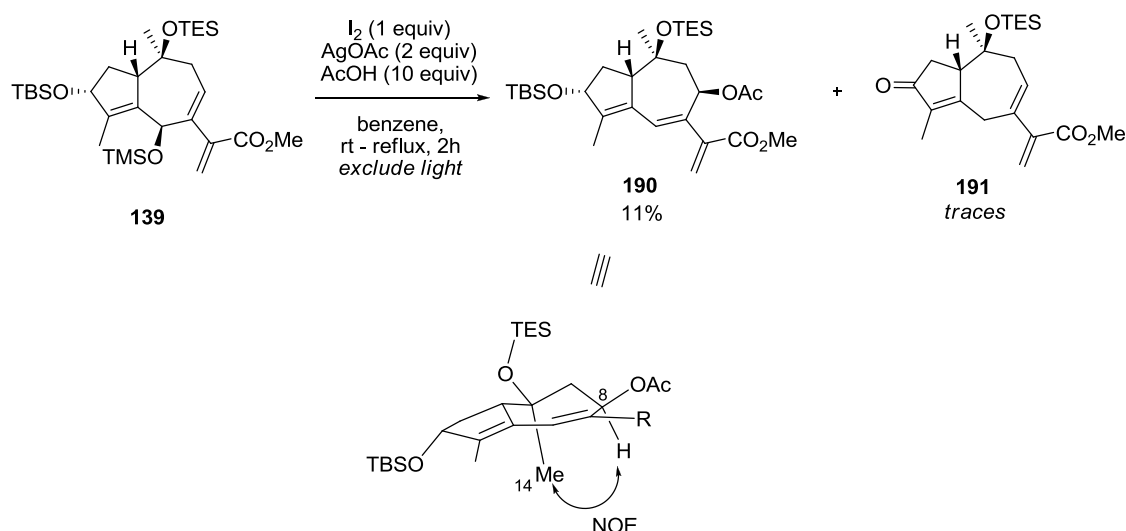
Scheme 85. Proposed Prévost pathway for bicyclic substrates **138-144**.

Subjecting TMS ether **139** to dry Prévost conditions did not lead to product **189** and only recovered starting material was isolated upon workup (Scheme 86).



Scheme 86. Trial dry Prévost reaction.

Inclusion of a large excess of acetic acid led to allyl-substituted acetate **190** as the only isolated product in poor yield (Scheme 87), and crude NMR revealed the presence of traces of product **191**. Perhaps the most surprising outcome was that the apparent S_N2' substitution reaction proceeded with *syn*-selectivity, as confirmed by an NOE between the C-8 proton and the C-14 methyl.



Scheme 87. Modified dry Prevost reaction conditions and observed NOE interactions in acetate **190**.

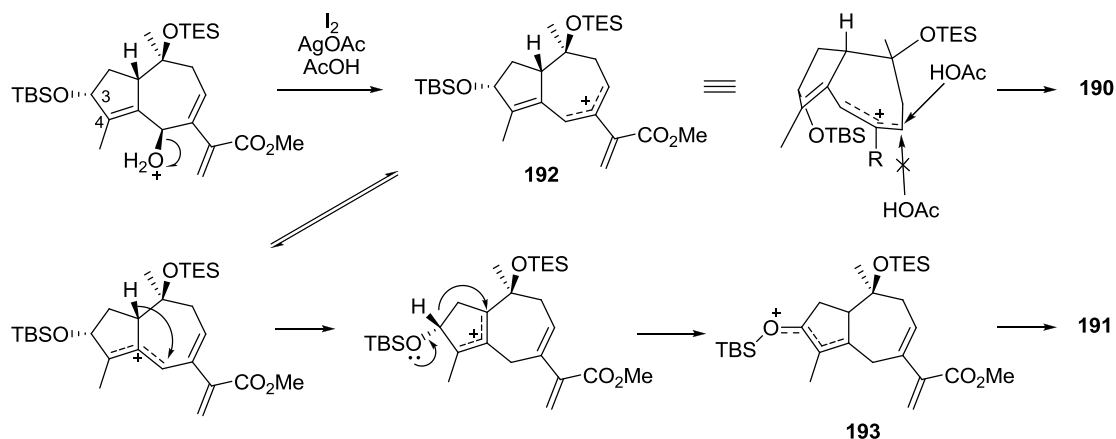
Direct S_N2' substitution reactions of allylic ethers are rare in literature, and are typically mediated by transition metal catalysts which can activate the electron-rich ethers towards substitution.¹⁵¹ Acid-mediated carbocation formation after *in situ* deprotection of the TMS ether might account for this behaviour, and the intermediate allylic carbocation would be expected to undergo nucleophilic addition on the convex face of **192** (Scheme 88). Ethers are known hydride shift donors to under Brønsted acid conditions.¹⁵² Analogous to the previous Overman-Pd(II) conditions, two consecutive [1,3]-hydride shifts to vinyl oxocarbenium ion **193** can be considered a possible explanation for the formation of product **191**, as intermediate **193** is heteroatom and conjugation stabilised.¹⁵³

¹⁵¹ a) Lalic, G.; Krinsky, J. L.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 4459.

b) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273.

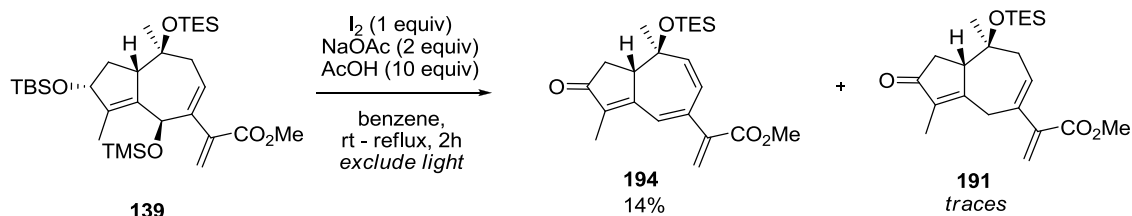
¹⁵² Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133*, 7696.

¹⁵³ Harmata, M.; Jones, D. E. *J. Org. Chem.* **1997**, *62*, 1578.



Scheme 88. Possible mechanism to acetate **190** and product **191**.

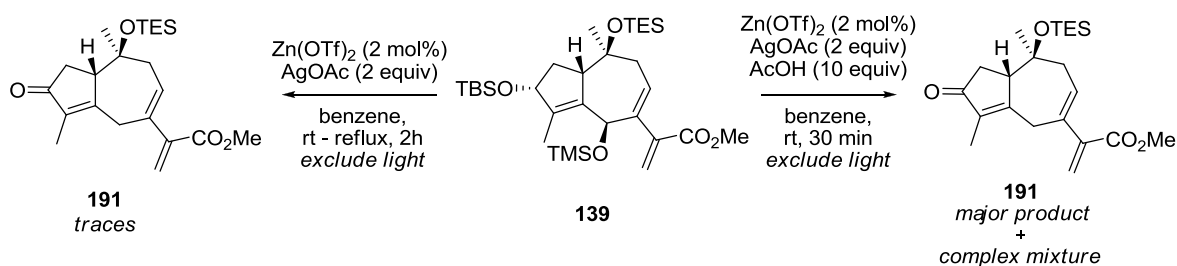
Although the use of silver(I) acetate led to the formation of acetate **190**, the use of sodium acetate led to the isolation of extended conjugated adduct **194** and trace amounts of **191** were present in the crude reaction mixture (Scheme 89). The exact mechanism for this reaction is not clear but the absence of silver acetate precludes preformed iodonium acetate in the reaction mixture, and the free molecular I_2 could potentially participate in concurrent halogenation/dehydrohalogenation of product **191**.¹⁵⁴



Scheme 89. Elimination under $I_2/NaOAc$.

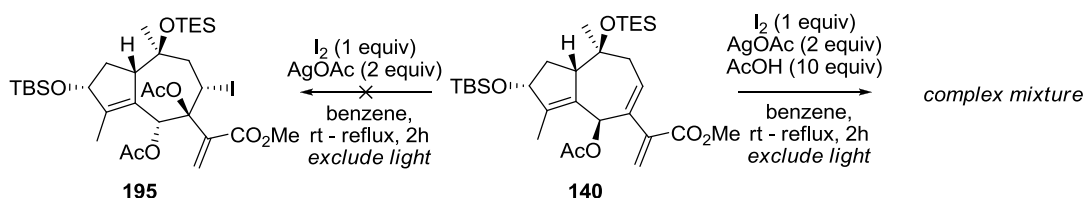
No reaction was observed before the addition of iodine, therefore variation of the Lewis acid in the reaction was tested. $Zn(OTf)_2$ without acetic acid led to a small conversion to adduct **191**, while reintroduction of the protic acid source led to quick conversion at room temperature, and produced a complex mixture with **191** visible in the crude NMR as a major product (Scheme 90).

¹⁵⁴ a) Jimenez-Aleman, G. H.; Schöner, T.; Montero-Alejo, A. L.; Brandt, W.; Boland, W. *Arkivoc* **2012**, 371.
b) Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. *J. Org. Chem.* **1995**, *60*, 1665.



Scheme 90. Lewis acid mediated elimination.

Analogous to the interrupted Prévost reaction during the synthesis of palytoxin (Scheme 83), attempts to access the desired reactivity from the Prévost reaction involved the use of anchimeric assistance from the preformed C-6 acetate in adduct **140**. However, none of the desired iodoacetate **195** was obtained when **140** was subjected to standard acetic acid mediated Prévost conditions (Scheme 91).



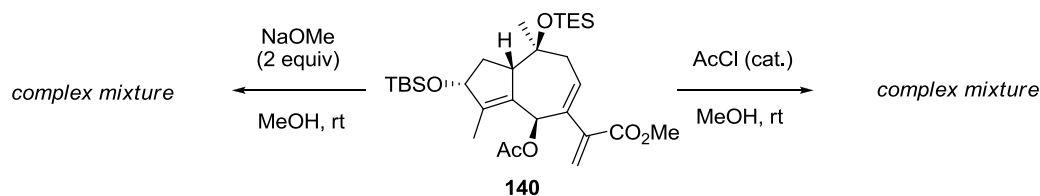
Scheme 91. Attempted use of pre-installed anchimeric assistance.

4.4.1.3 Modified substrates for C-7/8 oxidation

From previous experiments, it was determined that the methyl acrylate moiety presented many reactivity problems. As a relatively unhindered Michael acceptor, it is expected to be reactive under a wide range of acidic and basic conditions. In order to regulate this reactivity, it was decided to explore functionalisation of the pendent methyl acrylate. Direct lactonisation with catalytic acetyl chloride¹⁵⁵ did not furnish any of the desired adducts (Scheme 92). Similarly, attempts to perform lactonisation and concurrent addition of an oxygen nucleophile under basic conditions¹⁵⁶ yielded no identifiable products.

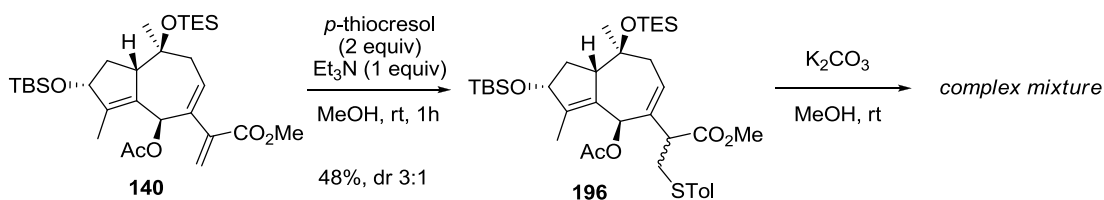
¹⁵⁵ Hon, Y. S.; Liu, Y. W.; Hsieh, C. H. *Tetrahedron* **2004**, *60*, 4837.

¹⁵⁶ Jia, Q. Q.; Wang, J. C.; Long, J.; Zhao, Y.; Chen, S. J.; Zhai, J. D.; Wei, L. B.; Zhang, Q.; Chen, Y.; Long, H. B. *Molecules* **2013**, *18*, 13061.



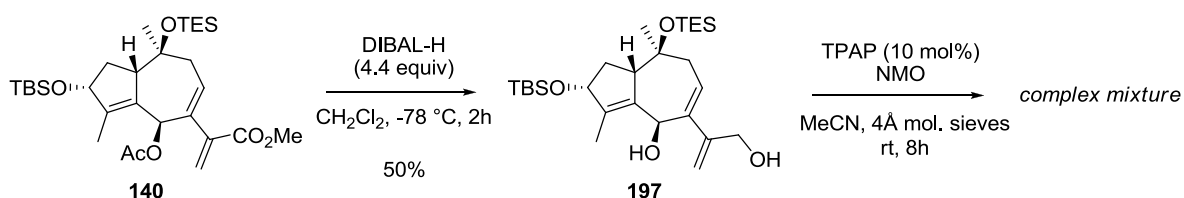
Scheme 92. Lactonisation attempts.

Michael addition of *p*-thiocresol to the thioether adduct **196** did succeed,¹⁵⁷ albeit in modest yield, and a mixture of inseparable diastereomers was obtained. However, subsequent lactonisation once again proved fruitless (Scheme 93). The relative configuration of the major diastereomer could not be established at this point.



Scheme 93. Michael addition/lactonisation.

Reduction of acetate **140** followed by selective oxidation of the primary alcohol **197** according to Massanet's protocol also failed to deliver the desired lactone (Scheme 94).⁶⁷



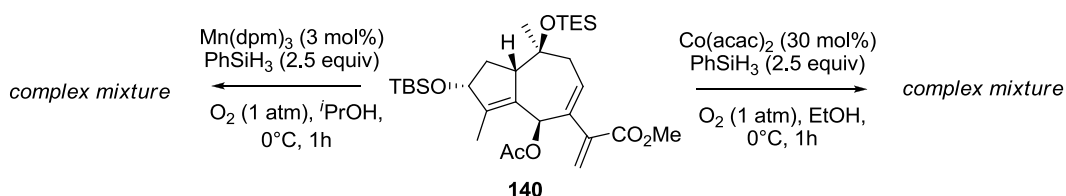
Scheme 94. Reduction/oxidation protocol.

Finally, attempts to perform the hydration across the conjugated alkene did not yield any discernible products either, despite the reported selective nature of the mild conditions employed (Scheme 95).¹⁵⁸

¹⁵⁷ Yang, H.; Gao, Y.; Qiao, X.; Xie, L.; Xu, X. *Org. Lett.* **2011**, *13*, 3670.

¹⁵⁸ a) Magnus, P.; Payne, A. H.; Waring, M. J.; Scott, D. A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725.

b) Wang, X.; Sun, W. Bin; Zou, J. P.; Lin, G. Q.; Sun, B. F. *Org. Biomol. Chem.* **2016**, *14*, 10581.

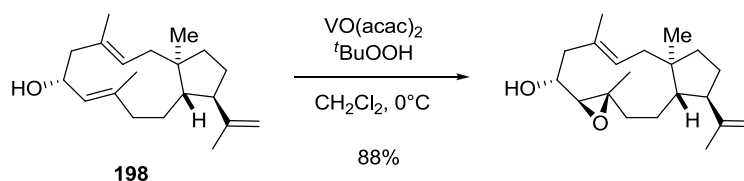


Scheme 95. Attempted hydration across methyl acrylate **140**.

4.4.2 Chemoselective epoxidation and derivatization of the epoxide

4.4.2.1 Directed epoxidation

Many oxidants can be used for the epoxidation of simple alkenes. However, hydroxyl-assisted epoxidation is commonly performed in the context of natural product synthesis with the use of metal catalysts as these reactions can be performed under mild conditions and often very selectively. To illustrate, during the synthesis of the clavularanes by Henry *et al.*, vanadium(IV)-catalysed epoxidation was able to distinguish between three separate olefins, as well as between the allylic and homoallylic positions in **198** (Scheme 96).¹⁵⁹



Scheme 96. Late-stage directed epoxidation during the total synthesis of the clavularanes.

In another, perhaps even more remarkable, selective epoxidation reaction, Nicolaou *et al.* were able to differentiate between two separate trisubstituted allylic alcohols in **199** as well as control α/β facial selectivity to a great degree (Scheme 97).¹⁶⁰ This reaction was entirely substrate controlled, therefore careful substrate selection beforehand was needed to ensure the right outcome.

¹⁵⁹ Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654.

¹⁶⁰ Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Fong, K. C.; Choi, H. S. *J. Am. Chem. Soc.* **2002**, *124*, 2190.

Table 11. Epoxidation conditions.

A
169 R = Me
200 R = *t*Bu
201 R = Bn

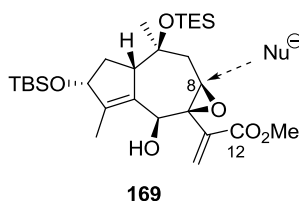
B
202 R = Me
203 R = *t*Bu
204 R = Bn

Entry	R	Cat. [mol%]	Oxidant [equiv]	<i>T</i> °C	solvent	Yield A[B]
1	Me	VO(acac) ₂ [2.5]	<i>t</i> BuOOH [1.5]	rt	PhH	67 [^a]
2	Me	VO(acac) ₂ [2.5]	<i>t</i> BuOOH [1.5]	rt	PhMe	0 [20]
3	Me	VO(acac) ₂ [2.5]	<i>t</i> BuOOH [1.5]	rt	CH ₂ Cl ₂	31 [n.d.]
4	Me	VO(<i>O</i> ^{<i>i</i>} Pr) ₃ [2.5]	<i>t</i> BuOOH [1.5]	rt	PhH	83 [0]
5	Me	Ti(<i>O</i> ^{<i>i</i>} Pr) ₄ [100]	<i>t</i> BuOOH [1.5]	-15	CH ₂ Cl ₂	n.r.
6	<i>t</i> Bu	VO(acac) ₂ [2.5]	<i>t</i> BuOOH [1.5]	rt	PhH	0 [73]
7	Bn	VO(acac) ₂ [2.5]	<i>t</i> BuOOH [1.5]	rt	PhH	39 [n.d.]
8	Bn	VO(acac) ₂ [2.5]	<i>t</i> BuOOH [1.5]	rt	CH ₂ Cl ₂	23 [n.d.]
9	Bn	VO(acac) ₂ [2.5]	CumeneOOH [1.5]	rt	PhH	^b
10	Bn	VO(<i>O</i> ^{<i>i</i>} Pr) ₃ [1.0]	<i>t</i> BuOOH [1.5]	rt	PhH	41 [n.d.]
11	Bn	VO(<i>O</i> ^{<i>i</i>} Pr) ₃ [2.5]	<i>t</i> BuOOH [1.5]	rt	PhH	8 [n.d.]

a) variable yield. b) Complex mixture of epoxides and starting material.

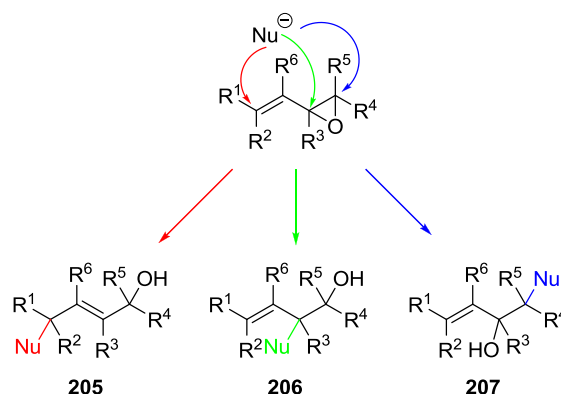
4.4.2.1 Inversion at C-8

It was envisioned that the correct stereochemical configuration at the C-7/8 stereocentres could be accomplished *via* an S_N2 nucleophilic attack on the C-8 site of epoxide **169** (Figure 22).

**Figure 22.** Envisaged nucleophilic attack on C-8.

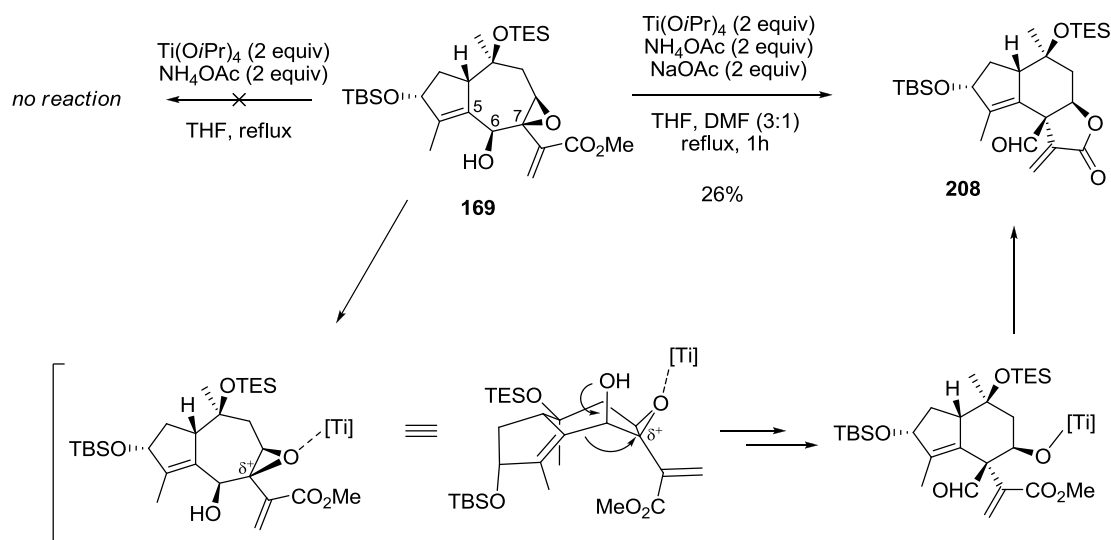
This could potentially be accomplished with either an internal or external nucleophile. Externally, the simple addition of a nucleophile could result in regioisomers **205-207**, (Scheme 98), and this is known to be highly dependent on the steric encumbrance of the

various reactive sites, the nature of the nucleophile and the stereoelectronic properties of the vinyl epoxide.¹⁶⁶



Scheme 98. Possible sites for nucleophilic attack on vinyl epoxides

Sharpless *et al.* has reported that 2,3-epoxy alcohols can be substituted regioselectively with a wide range of heteroatom nucleophiles using titanium isopropoxide as a Lewis acid mediator.¹⁶⁷ Under Sharpless' conditions, epoxide **169** is resistant to nucleophilic substitution (Scheme 99). Surprisingly, when more forceful conditions are applied (DMF, reflux), an unexpected semi-pinacol rearrangement occurs, with a 1,2-migration of the C-5/6 bond to the C-7 position to form aldehyde **208**.

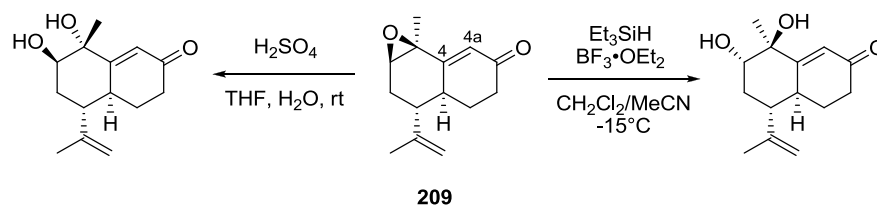


Scheme 99. Titanium isopropoxide mediated semi-pinacol rearrangement.

¹⁶⁶ He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037.

¹⁶⁷ Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

An unusual example of epoxide opening has been reported by Ducrot *et al.* whereby epoxide **209** undergoes Lewis acid-mediated ring opening with inversion of configuration on the less stable carbocationic site (Scheme 100) in the presence of triethylsilane.¹⁶⁸ This was in contrast to Brønsted acid conditions which furnished the expected inverted *anti*-diol. The mechanism for this unusual behaviour has not been elaborated, but hydrogenation of the C-4/4a olefin had no effect on the course of the reaction.



Scheme 100. Epoxide cleavage by Ducrot *et al.*

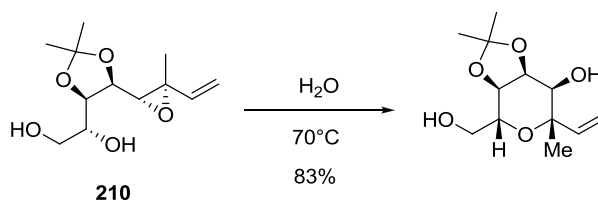
Unfortunately, epoxide cleavage of substrate **169** under Ducrot's conditions did not yield the expected adduct, but instead furnished an unidentified adduct. The presence of a clear aldehyde signal (^1H δ 9.82 ppm, dd $J = 3.7, 2.5$ Hz, CDCl_3) suggested that the reaction had once again proceeded along a semi-pinacol type rearrangement. However, the unusual splitting pattern and a nominal mass peak of m/z 276 pointed to a either a different mechanistic pathway or a more extensive rearrangement, and the corresponding coupling signals could not be identified in the spectrum. Unfortunately, analysis was hampered by the rapid decomposition of the product during standard purification techniques and prolonged storage in deuterated chloroform.

Water has been known to act as a general acid catalyst and nucleophile in epoxide cleavage reactions,¹⁶⁹ and has been used by Nicolaou *et al.* to great effect during the synthesis of the QRSTU domain of maitotoxin to promote the intramolecular cyclisation of epoxy alcohol **210** when traditional Brønsted acid catalysis failed to give the product in acceptable yields (Scheme 101).¹⁷⁰ The high temperatures are not only required to promote the reaction but also to ensure sufficient amounts of the usually non-polar substrates are dissolved in the aqueous media for the reaction to occur.

¹⁶⁸ Beauhaire, J.; Ducrot, P. H.; Simon, I. *Synth. Commun.* **1995**, 25, 3015.

¹⁶⁹ Wang, Z.; Cui, Y. T.; Xu, Z. B.; Qu, J. *J. Org. Chem.* **2008**, 73, 2270.

¹⁷⁰ Nicolaou, K. C.; Gelin, C. F.; Seo, J. H.; Huang, Z.; Umezawa, T. *J. Am. Chem. Soc.* **2010**, 132, 9900.



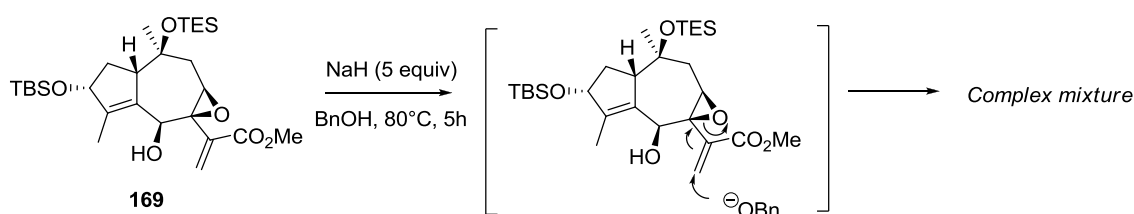
Scheme 101. Hot water promoted epoxide cleavage.

Unfortunately, none of the water/base conditions tested were sufficient to effect epoxide cleavage, except when organic solvents are included. However, these conditions degrade the starting material, with nothing being recovered (Table 12),

Table 12. Hot water promoted epoxide opening.

<p style="text-align: center;">169</p>			
Entry	Conditions	Temp (°C)	Yield (%)
1	H ₂ O	60	n.r.
2	H ₂ O	100	n.r.
3	H ₂ O, NaHCO ₃	100	n.r.
4	H ₂ O, KOH	100	n.r.
5	H ₂ O, DMSO, KOH	100	degradation

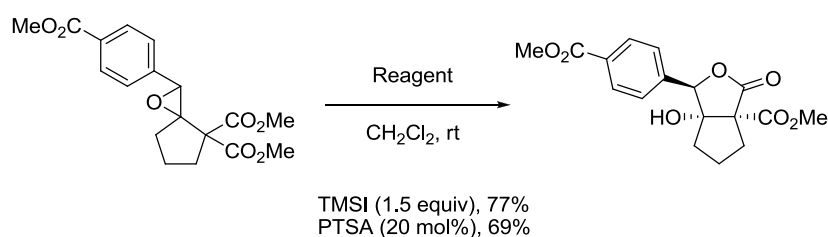
A final attempt at external nucleophilic opening of epoxide **169** was made using benzyl alcohol and sodium hydride (Scheme 102). This gave a rather complex mixture of products but crude NMR analysis indicated that the S_N2' nucleophilic attack had predominated, consistent with a sterically hindered vinyl epoxide, as a mixture of *E/Z* isomers.



Scheme 102. Benzyl alcohol external nucleophilic opening of epoxide **169**.

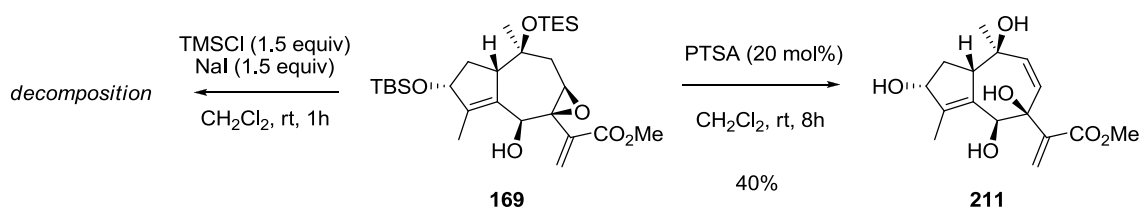
In order to hopefully limit the reactive site to C-8, internal nucleophiles centred on C-12 were then explored. Balme *et al.* had shown that epoxy-diester could undergo cyclisation

mediated by either trimethylsilyliodide or *p*-toluenesulfonic acid (PTSA) to the corresponding δ -hydroxy- γ -lactones (Scheme 103).¹⁷¹



Scheme 103. Dealkylative cyclisation of epoxy-diester.

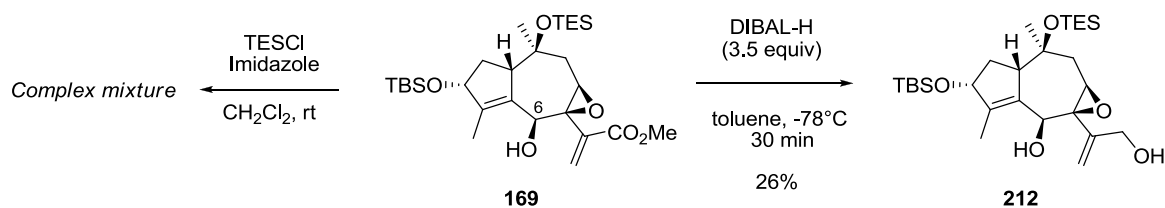
Subjecting epoxide **169** to both these conditions did not result in recovery of the desired adduct (Scheme 104). While the *in situ* formation of trimethylsilyl iodide resulted in complete degradation of the starting material, the use of catalytic amounts of PTSA resulted in the formation of byproduct **211** in poor yield after column chromatography. This derivative also proved to be rather unstable under atmospheric conditions and did not survive long enough to be fully analysed, having decomposed after several hours in deuterated solvent. Thus, the proposed structure is based on incomplete spectroscopic analysis.



Scheme 104. Attempted dealkylative cyclisation into epoxide **169**.

Internal nucleophilic attack onto the C-7/8 epoxide was attempted using an alcohol as a nucleophile. Selective reduction of the epoxyester **169** provided diol **212** in low yield (Scheme 105). A cursory solvent screen (CH_2Cl_2 , hexane, toluene) showed that toluene was the superior solvent for this reaction, but optimisation of these conditions is needed.

¹⁷¹ Pehlivan, L.; Jacolot, M.; Coia, N.; Monteiro, N.; Bouyssi, D.; Balme, G. *Tetrahedron Lett.* **2011**, 52, 4716.



Scheme 105. Reduction of the ester moiety and attempted temporary silyl protection of the C-6 alcohol.

The low yield of this reaction is likely attributable to adjacent C-6 alcohol to the C-7/8 epoxide, directing the incoming Al-hydride reagent to reduce the epoxide instead,¹⁷² causing unwanted side-reactions. An attempt to temporarily protect the C-6 alcohol of **169** failed (TESCl, imidazole, CH₂Cl₂), most likely due to another semi-pinacol type reaction, as silyl halides are known promoters of the rearrangement of 2,3-epoxy alcohols.¹⁷³ Although the mass spectrum analysis indicated the addition of a triethylsilyl group (m/z calc 675.3903, found 675.3895), assignment of spectroscopic data was difficult due to the appearance of a mixture of inseparable isomeric products.

Alcohol **212** was then subjected to standard deprotonation conditions (NaH, DMF) to try and effect cyclisation to the desired ether. However, when the reaction was heated, a complex mixture of products was formed. It should be noted that the NaH and DMF reagent/solvent combination has previously been found to be problematic under certain circumstances.¹⁷⁴ The use of rhodium carbonyl chloride dimer¹⁷⁵ as the reagent also gave intractable mixtures.

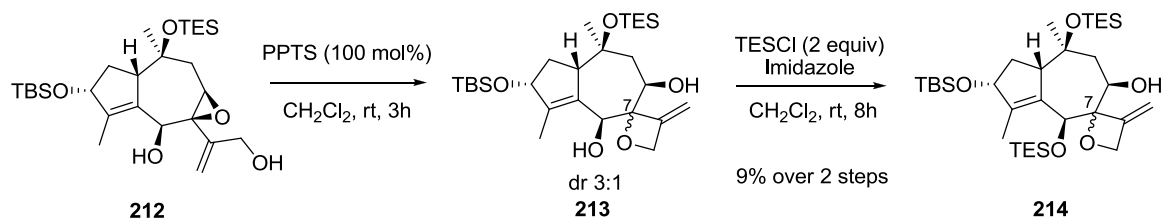
Under mild acidic conditions, however, a diastereomeric mixture of oxetane **213** is obtained, presumably through the formation of a stabilised vinyl carbocation intermediate which is attacked by the free pendent alcohol (Scheme 106). Oxetane **213** was difficult to separate and characterise, but derivatisation to give the persilylated adduct **214** provided a clean sample after chromatography that could be identified. Unfortunately the configuration at C-7 of the major product could not be established.

¹⁷² Krishna, P. R.; Kadiyala, R. R. *Tetrahedron Lett.* **2010**, 51, 4981.

¹⁷³ Song, Z. L.; Fan, C. A.; Tu, Y. Q. *Chemical Reviews.* **2011**, 111, 7523.

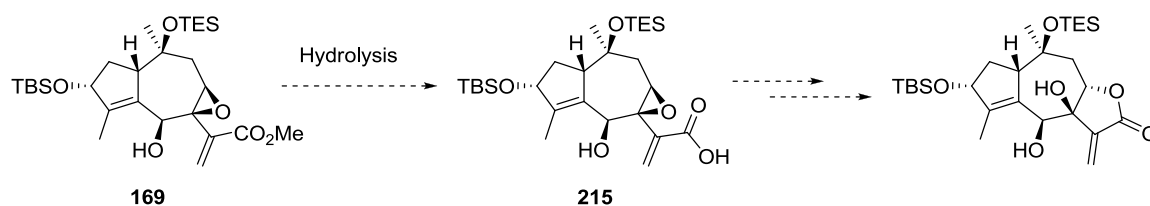
¹⁷⁴ Heseck, D.; Lee, M.; Noll, B. C.; Usher, J. F.; Mobashery, S. *J. Org. Chem.* **2009**, 74, 2567.

¹⁷⁵ Ha, J. Du; Shin, E. Y.; Kang, S. K.; Ahn, J. H.; Choi, J. K. *Tetrahedron Lett.* **2004**, 45, 4193.



Scheme 106. Oxetane formation under acidic conditions.

Our attention then turned to the hydrolysis of ester **169** as a means of obtaining the free acid **215**, which could hopefully be used to affect epoxide cleavage (Scheme 107).



Scheme 107. Proposed route to lactonisation using free acid **215**.

A range of hydrolysis conditions were explored on methyl ester **169** (Table 12). Common basic conditions using sodium and lithium hydroxide (Entries 1 and 2), proved too harsh to affect the desired transformation, resulting only in decomposition. The use of non-basic *in situ* formed lithium hydroperoxide has previously been found to effect epoxide cleavage and de-esterification through anchimeric assistance of an ester moiety.¹⁷⁶ However, these conditions only resulted in decomposition of adduct **169** (Entry 3). Mild anhydrous de-esterification with dimethylaluminium methyltellurate¹⁷⁷ or trimethyltin hydroxide¹⁶¹ also did not effect the desired cleavage (Entries 4 and 5).

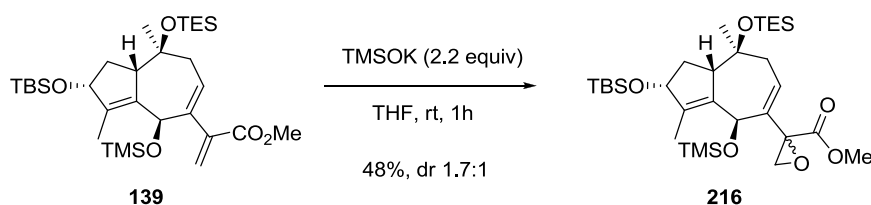
¹⁷⁶ Morzycki, J. W.; Gryszkiewicz, A.; Jastrz, I. *Tetrahedron* **2001**, 57, 2185.

¹⁷⁷ Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Tetrahedron Lett.* **2005**, 46, 4589.

Table 12. Hydrolysis conditions.

Entry	Conditions	Temp (°C)	Time	Yield (%)
1	NaOH, THF/H ₂ O	0	1h	degradation
2	LiOH, THF/H ₂ O	0	1h	degradation
3	LiOH, H ₂ O ₂ , EtOH	rt	1h	degradation
4	(Me ₂ AlTeMe) ₂ , toluene	rt	5h	degradation.
5	Me ₃ SnOH (10 equiv), toluene	80	72h	n.r.

Additionally, a hydrolysis attempt was made to cleave the ester in epoxide precursor **139** with potassium trimethylsilanolate.¹⁷⁸ Although this reaction did not cleave the ester to give the acid, it did effect an unusual epoxidation reaction of the C-11/13 olefin (Scheme 108) to epoxide **216**. A literature search revealed no comparable transformation, but it is possible that the reagent had oxidised to the corresponding peroxide at some point, although a potassium iodide test of the reagent proved negative.

**Scheme 108.** Unusual epoxide formation using trimethylsilanolate.

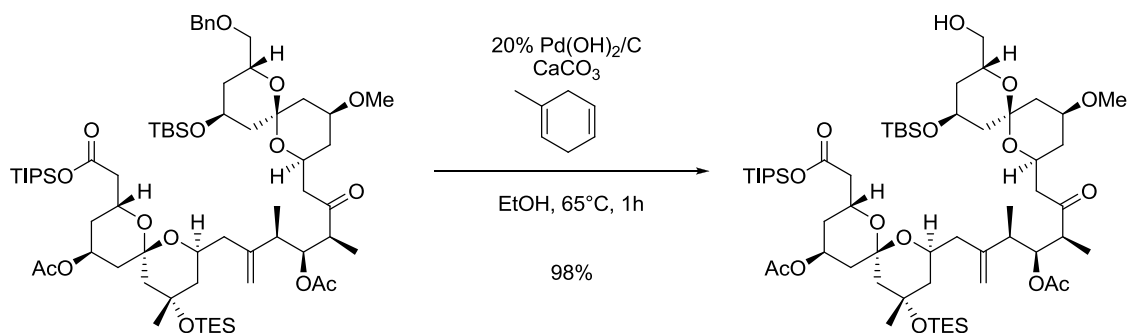
Finally, our attention turned to epoxy benzyl ester **201** as a substrate that would allow de-esterification under mild and neutral conditions, primarily through hydrogenolysis, as harsher conditions such as the use of FeCl₃¹⁷⁹ resulted in decomposition.

Many different catalytic systems exist for the hydrogenolysis of benzyl ethers and esters, and many were developed to allow the desired transformation to be accomplished in complex poly-functionalised systems. For the synthesis of spongistatin 1, Smith III *et al.*

¹⁷⁸ Gilbert, B. A.; Tan, E. W.; Pérez-Sala, D.; Rando, R. R. *J. Am. Chem. Soc.* **1992**, *114*, 3966.

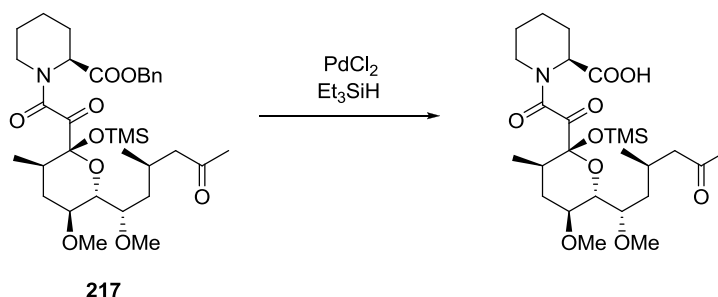
¹⁷⁹ Davies, T. J.; Jones, R. V. H.; Lindsell, W. E.; Miln, C.; Preston, P. N. *Tetrahedron Lett.* **2002**, *43*, 487.

employed a transfer hydrogenation system that successfully cleaved a primary benzyl ether in the presence of many sensitive functional groups (Scheme 109).¹⁸⁰



Scheme 109. Selective hydrogenolysis during the synthesis of spongistatin 1.

During the synthesis of the C-10/17 unit of FK-506, Rupprecht *et al.* used homogeneous palladium catalysis to affect hydrogenolysis of adduct **217** as part of a multi-step sequence and these conditions are known to be compatible with simple olefins (Scheme 110).^{181,182}



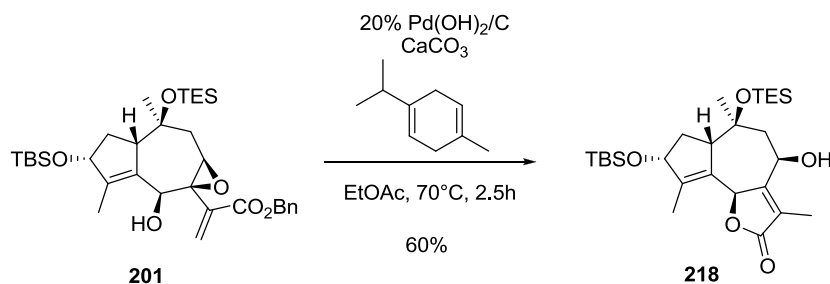
Scheme 110. Homogeneous hydrogenolysis conditions.

When heterogeneous conditions were employed at room temperature, the substrate **201** failed to react and reactivity was only observed at higher temperatures (Scheme 111). The sole isolable product from this reaction was assigned as lactone **218**, although this could not be confirmed by mass spectrometry due to a fault.

¹⁸⁰ Smith III, A. B.; Sfougataakis, C.; Risatti, C. A.; Sperry, J. B.; Zhu, W.; Doughty, V. A.; Tomioka, T.; Gotchev, D. B.; Bennett, C. S.; Sakamoto, S. *Tetrahedron* **2009**, 65, 6489.

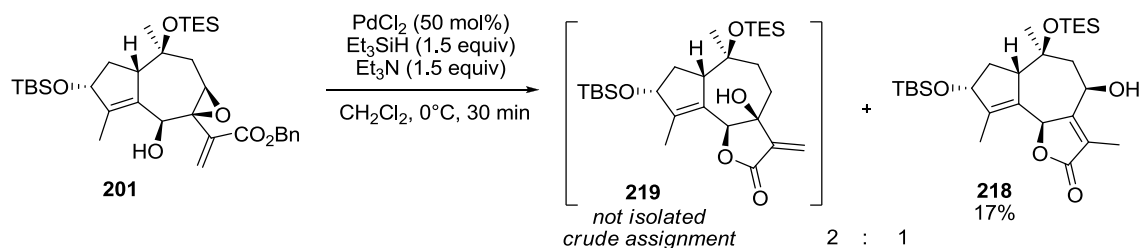
¹⁸¹ Rupprecht, K. M.; Baker, R. K.; Boger, J.; Davis, A. A.; Hodges, P. J.; Kinneary, J. F. *Tetrahedron Lett.* **1998**, 39, 233.

¹⁸² Sakaitani, M.; Kurokawa, N.; Ohfuné, Y. *Tetrahedron Lett.* **1986**, 27, 3753.



Scheme 111. Heterogeneous transfer hydrogenation.

Under homogeneous conditions, two major products are formed (Scheme 112). The first product is the aforementioned lactone **218**, but the second (major) product could not be identified. The crude product spectra were complex and no mass spectrometry was available. High loading of palladium chloride (50 mol%) is needed for this product to appear as the major product in an otherwise complex mixture, and based on the reactivity pattern that forms lactone **218** a tentative assignment of **219** was made.



Scheme 112. Homogenous reduction conditions.

The reason for this assignment was that reductive epoxide ring openings catalysed by Pd(0) and Pd(II) are known to occur with selectivity for substitution at the allylic position to generate homoallylic alcohols in the absence of significant steric encumbrance.¹⁸³ However, since **218** was obtained as the major product under heterogeneous conditions, it indicated that significant steric interaction forced the S_N2' reduction pathway, and that therefore the direct S_N2 hydrogenolysis at the homoallylic position also became more likely. Associated ^1H signals were those of the methylene protons (δ 6.33, 5.68). The disappearance of the benzylic protons, the appearance of H-6 (δ 4.84, s),¹⁸⁴ and the

¹⁸³ a) Yokoyama, H.; Hayashi, Y.; Nagasawa, Y.; Ejiri, H.; Miyazawa, M.; Hirai, Y. *Tetrahedron* **2010**, 66, 8458.

b) Pujari, S. A.; Gowrisankar, P.; Kaliappan, K. P. *Chem. Asian J.* **2011**, 6, 3137.

c) Gowrisankar, P.; Pujari, S. A.; Kaliappan, K. P. *Chem. Eur. J.* **2010**, 16, 5858.

¹⁸⁴ Sohoni, J. S.; Rojatar, S. R.; Kulkarni, M. M.; Dhaneshwar, N. N.; Tavale, S. S.; Gururow, T. N.; Nagasampagi, B. A. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 0, 157.

remaining H-3 (δ 4.39, d app) indicated that the C-4/5 olefin was still intact. Any attempt at standard purification resulted only in recovery of lactone **218**, presenting difficulty in analysing the small quantity of material that had been synthesised.

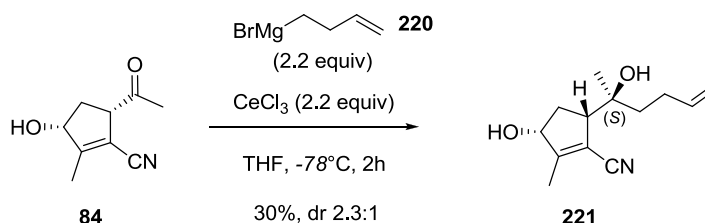
4.5 Conclusions

An array of oxidative procedures were applied to the bicyclic adducts **138-144** in order to target the C-7/8 olefin chemoselectively. Vanadium-catalysed directed epoxidation proved to be suitable for diastereoselective epoxidation of the allylic alcohols **138** and **144**. Elaboration on epoxy alcohols **169** and **201** was generally hampered by the high reactivity of the vinyl epoxide in combination with a good Michael acceptor, and the most promising conditions for further study are those that involve mild hydrogenolysis of **201** as demonstrated through heterogeneous Pd-catalysed formation of [5,7,5] tricyclic lactone **218**.

Chapter 5: [5,8] thapsigargin analogues

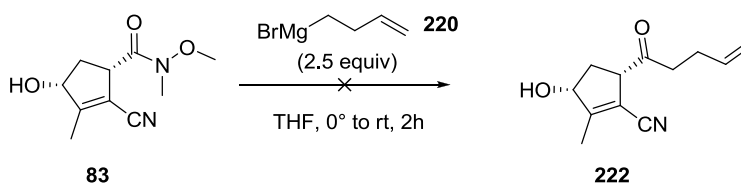
5.1 Synthesis of a [5,8] bicyclic structure

An efficient enantioselective synthesis of common ketone intermediate **84** had been established and so a route could now be devised to exemplify the flexibility of the chosen synthetic strategy in the context of varying ring sizes. The first challenge was to install the C-10 stereocentre with hopefully a similar efficiency compared with the allyl homologue. Subjecting ketone **84** to Grignard reagent **220** in the presence of dry cerium(III) chloride resulted in a disappointing yield and diastereomeric ratio of adduct **221** in contrast to previous results (Scheme 113).



Scheme 113. Synthesis of homoallyl homologue **221**.

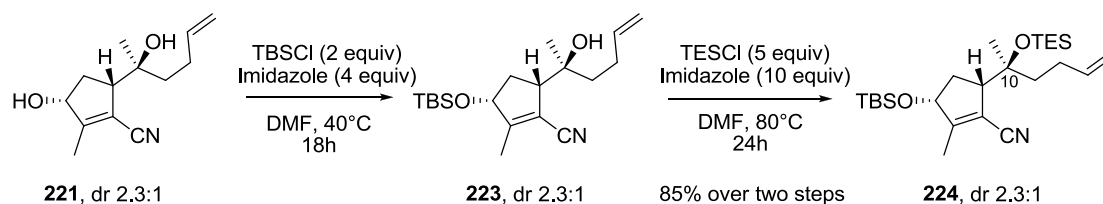
This reaction has scope for optimisation as the nature of the allylmagnesium Grignard reagent is markedly different compared to non-allylic reagents.¹⁰² The presence of β -hydrogens on Grignard reagents is known to cause many side reactions as the substrates and nucleophiles become more hindered, and therefore the reaction might benefit more from Hatano's conditions developed for such systems (Scheme 54).¹¹⁰ The direct addition of Grignard **220** to Weinreb amide **83** did not proceed to give the expected product **222** (Scheme 114).



Scheme 114. Attempted nucleophilic attack onto Weinreb amide **83**.

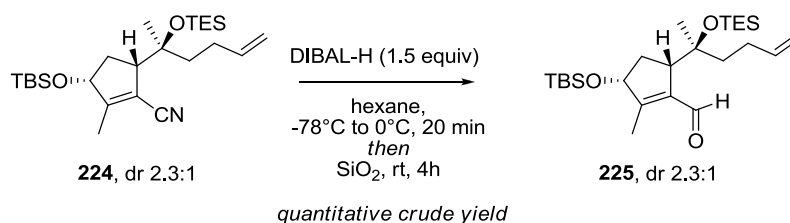
Mono-protection of diol **221** proceeded without incident, but the two epimeric products could not be separated by standard chromatographic techniques and compound **223** was

elaborated as a mixture of diastereomers for the rest of the synthesis (Scheme 115). The protection of the C-10 tertiary alcohol **223** also proceeded efficiently. The configuration at the C-10 stereocentre of the major diastereomer of **221** could not be definitively established at this point and is proposed based on the reaction of ketone **84** to give the allylated homologue **103**. Definitive NOE correlations have also not yet been established on later cyclised derivatives.



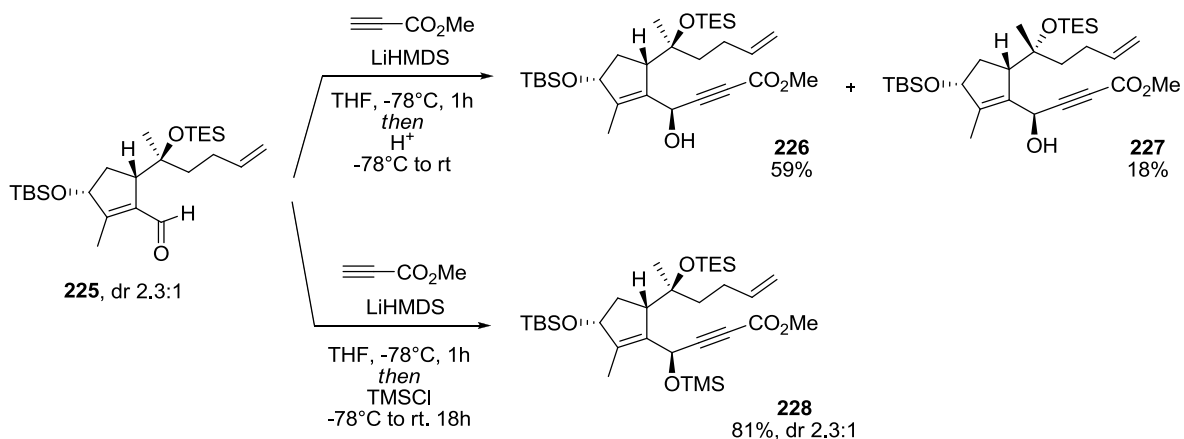
Scheme 115. Sequential double protection of diol **221**.

This synthetic intermediate **224** is stable to long term storage under ambient atmosphere and is therefore a good synthetic platform for subsequent exploration of the synthesis of further [5,8] bicyclic systems. Nitrile reduction followed by the previous mild hydrolysis conditions furnished the crude aldehyde **225** quantitatively and with sufficient purity for continuation of the synthesis (Scheme 116).



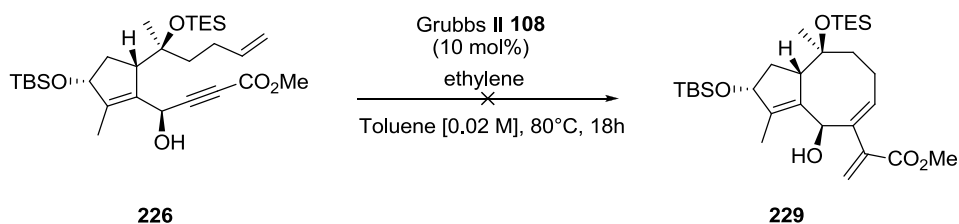
Scheme 116. Nitrile reduction under mild hydrolysis.

Gratifyingly, alkynyl addition to aldehyde **225** proceeded as expected with near complete stereocontrol for both diastereomers. At this stage the diastereomers of free alcohols **226** and **227** could be separated using standard chromatographic methods. However, the TMS protected variant **228** was still an inseparable mixture (Scheme 117).



Scheme 117. Protected and unprotected alkynylation products.

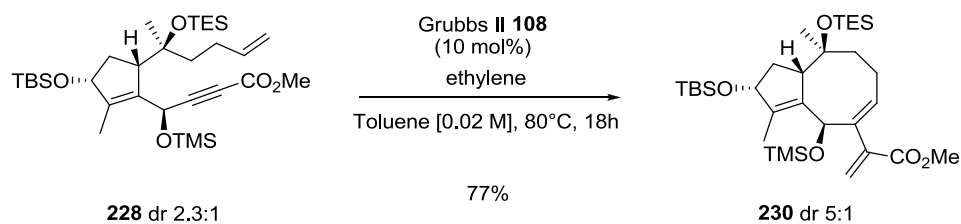
The RCEYM protocol was then attempted on the free alcohol **226**, but this did not proceed to give the expected bicycle **229**, and only degradation products were obtained (Scheme 118).



Scheme 118. RCEYM failure with propargylic alcohols.

8-Membered carbocycles are known to be difficult to synthesise by RCM due to the development of increased ring strain in the product and transannular interactions in the cyclisation transition state.¹⁸⁵ This problem, in addition to the earlier explored effect of the propargylic alcohol, can reasonably explain the near complete failure of the expected reaction. However, when the metathesis reaction conditions were applied to protected adduct **228**, the cyclisation proceeded smoothly to the desired bicyclic triene **230** (Scheme 119).

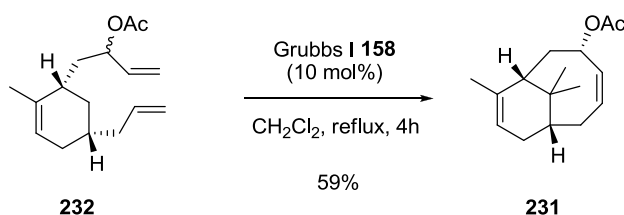
¹⁸⁵ Michaut, A.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5740.



Scheme 119. Successful application of RCYEM conditions to the synthesis of [5,8] bicycles.

The use of normal catalyst loading and temperatures was surprising considering the general use of high loadings in eight-membered rings to combat reactivity problems. The presence of a pre-existing ring system is likely to be a major factor in the relative ease of cyclisation as it physically forces the reactive alkene and alkyne in close proximity to each other.¹⁸⁶ The removal of the coordinating ability of the propargyl alcohol and the introduction of a Thorpe-Ingold effect due to the bulky silyl ether also likely assisted the reaction.¹⁸⁷

Albeit unexpected, a welcome reactivity difference was observed between the two starting isomers, leading to an increased diastereomeric ratio. Numerous examples of such effects exist in literature and especially natural product synthesis. For instance during the synthesis of the taxoid A,B-ring fragments, Blechert *et al.* constructed bicyclic structure **231** as one stereoisomer after reacting the starting diastereomeric mixture **232** under Grubbs metathesis conditions (Scheme 120), while the undesired diastereomer underwent dimerisation.



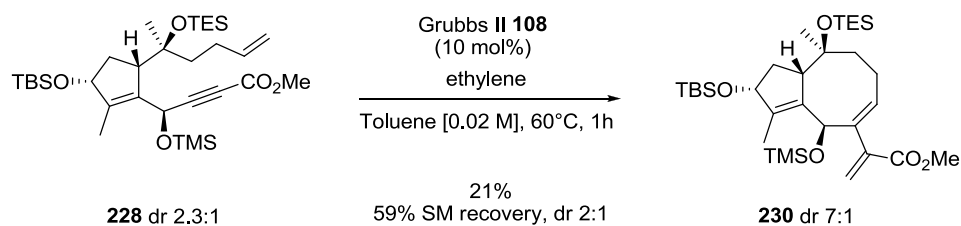
Scheme 120. Ring-closing metathesis during the synthesis of taxoid fragments by Blechert *et al.*

Carrying out the earlier reaction of TMS ether **228** at a lower temperature and interrupting the incomplete reaction formation resulted in the isolation of product **230** with an even

¹⁸⁶ Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

¹⁸⁷ Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869.

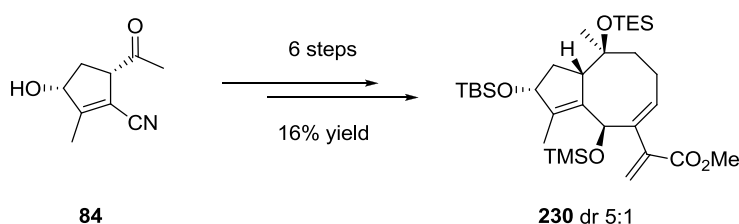
higher diastereomeric ratio as well as recovery of a depleted ratio of starting material diastereomers (Scheme 121)



Scheme 121. Lower temperature RCEYM reaction showing an increased dr.

5.2 Conclusions

Unnatural thapsigargin core-structural homologue **230** has been synthesised in 6 steps from common ketone intermediate **84** using the key ring-closing ene-yne metathesis step with similar efficiency compared to the natural core structures in previous chapters (Scheme 122).

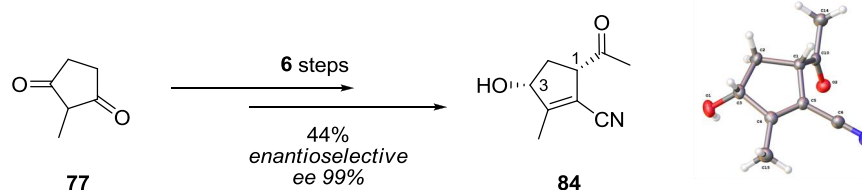


Scheme 122. Completion of a [5,8] thapsigargin core homologue.

This is the first foray into the bicyclic core modification of thapsigargin, taking advantage of a pre-installed five-membered ring to easily access the otherwise challenging [5,8] fused bicyclic system.

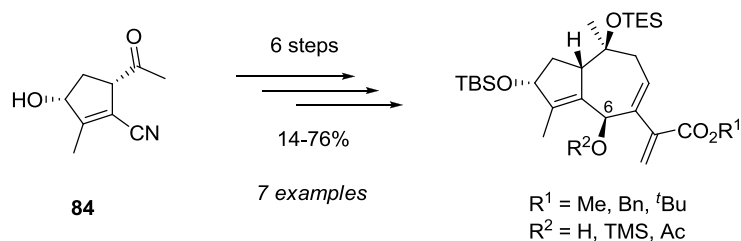
Conclusions and perspectives

Building on previous methodology, this work has expanded the scope of the synthetic strategy towards versatile cyclopentenol building block **84** to include an enantioselective pathway towards the (1*S*,3*R*) natural thapsigargin configuration (Scheme 123).



Scheme 123. Summary of results towards ketone **84**.

The key allylation reaction of ketone **84** and subsequent steps have been markedly improved and have also furnished several new [5,7]-bicyclic structures. The protected C-6 allylic alcohol analogues were the most efficient way to rapidly construct the guaianolide carbon skeleton (Scheme 124) as the free alkynyl alcohols suffered from a large drop in yield during RCEYM reactions.



Scheme 124. Construction of [5,7]-bicycles.

These bicyclic adducts were then used to explore a range of synthetic strategies towards the fully oxidised skeleton of thapsigargin **1** and nortrilobolide **19**. Unfortunately, many of the substrates used in these processes proved highly sensitive and so precise modulation of reaction conditions were necessary to obtain any desired reactivity. The general conclusion is that epoxides of type **233** (Figure 23) are sensitive to acidic conditions and can be expected to exhibit unexpected reactivity and probable decomposition under such conditions. They are, however, generally unreactive to mildly basic conditions, and near neutral conditions can also be applied to effect desired transformations, as is the case with hydrogenolysis of **201** to give the adduct **218**.

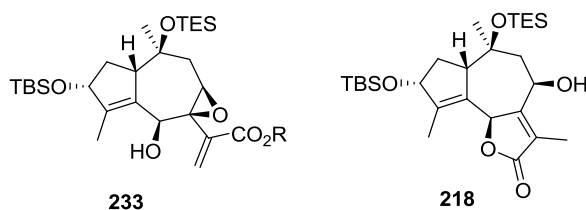
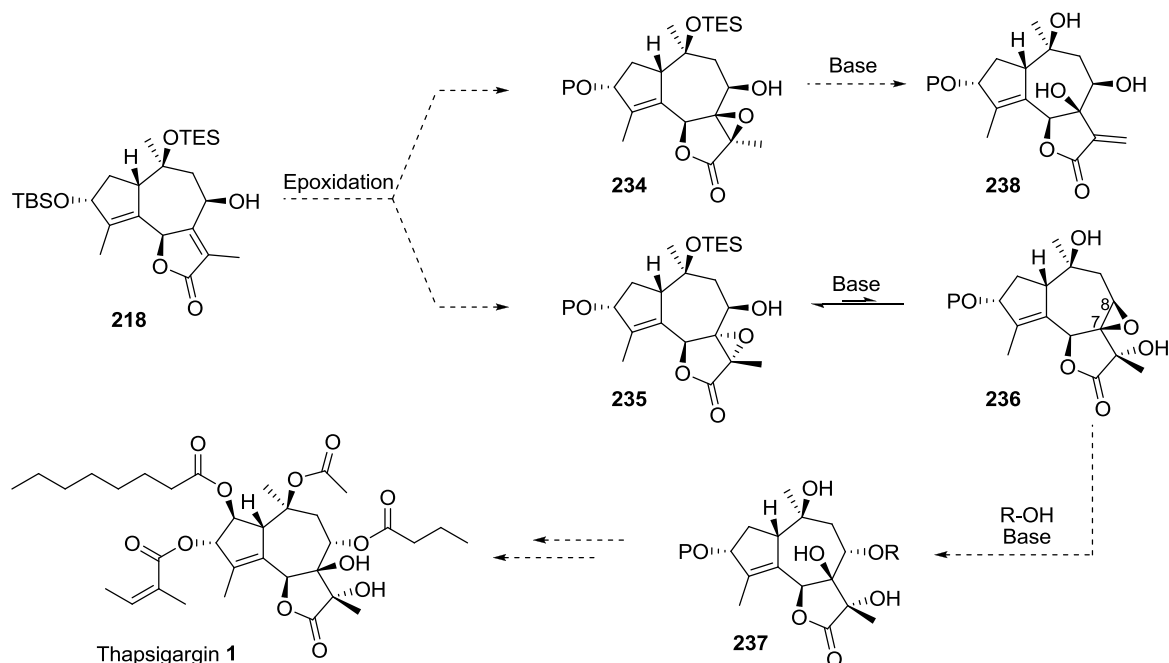


Figure 23. Possible intermediates towards the total synthesis of Tg **1**.

From here we can envisage a route to the desired natural compounds. Building on the work of Massanet,¹⁸⁸ unsaturated lactone **218** could be converted into either epoxide **234** or **235** under basic conditions, depending on facial selectivity (Scheme 125). In the event that epoxide **235** is the major stereochemical outcome of the epoxidation, it can be envisaged that access to the correct configuration of the C-7/8 hydroxyls could be provided by a Payne rearrangement to epoxyalcohol isomer **236** followed by nucleophilic opening at the less substituted C-8 position to an advanced intermediate **237**.¹⁸⁹ Although epoxide **235** is favoured in the equilibrium under basic isomerisation conditions, steric factors would favour nucleophilic opening of isomer **236**, thus the reaction would be expected to be under Curtin-Hammett conditions, assuming isomerisation is fast compared to epoxide opening.

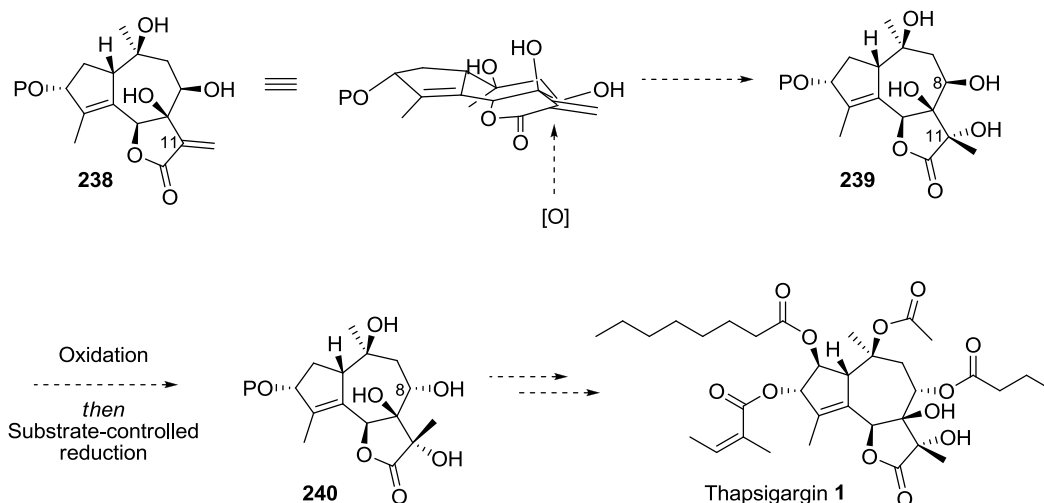


Scheme 125. Suggested approaches to Tg **1** from unsaturated lactone **218**.

¹⁸⁸ Coladol, I. G.; Alonso, M. S.; Hernández-Galán, R.; Madero, J. G.; Massanet, G. M. *Tetrahedron* **1994**, *50*, 10531.

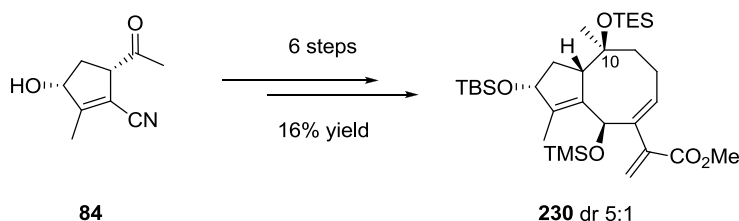
¹⁸⁹ Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378.

Base-mediated elimination and opening of the opposite epoxylactone **234** could be used to access methylene lactone **238**. The relatively flat conformation of methylene lactone **236** could allow for hydration across the desired face of the methylene lactone to the C-11 tertiary alcohol **239**, which could be taken on to Tg **1** after establishing the correct C-8 stereochemistry *via* a sequential oxidation-procedure to tetrol **240**, analogous to the strategy previously employed by Evans (Scheme 126).⁶⁹



Scheme 126. Alternative strategy to Tg **1**.

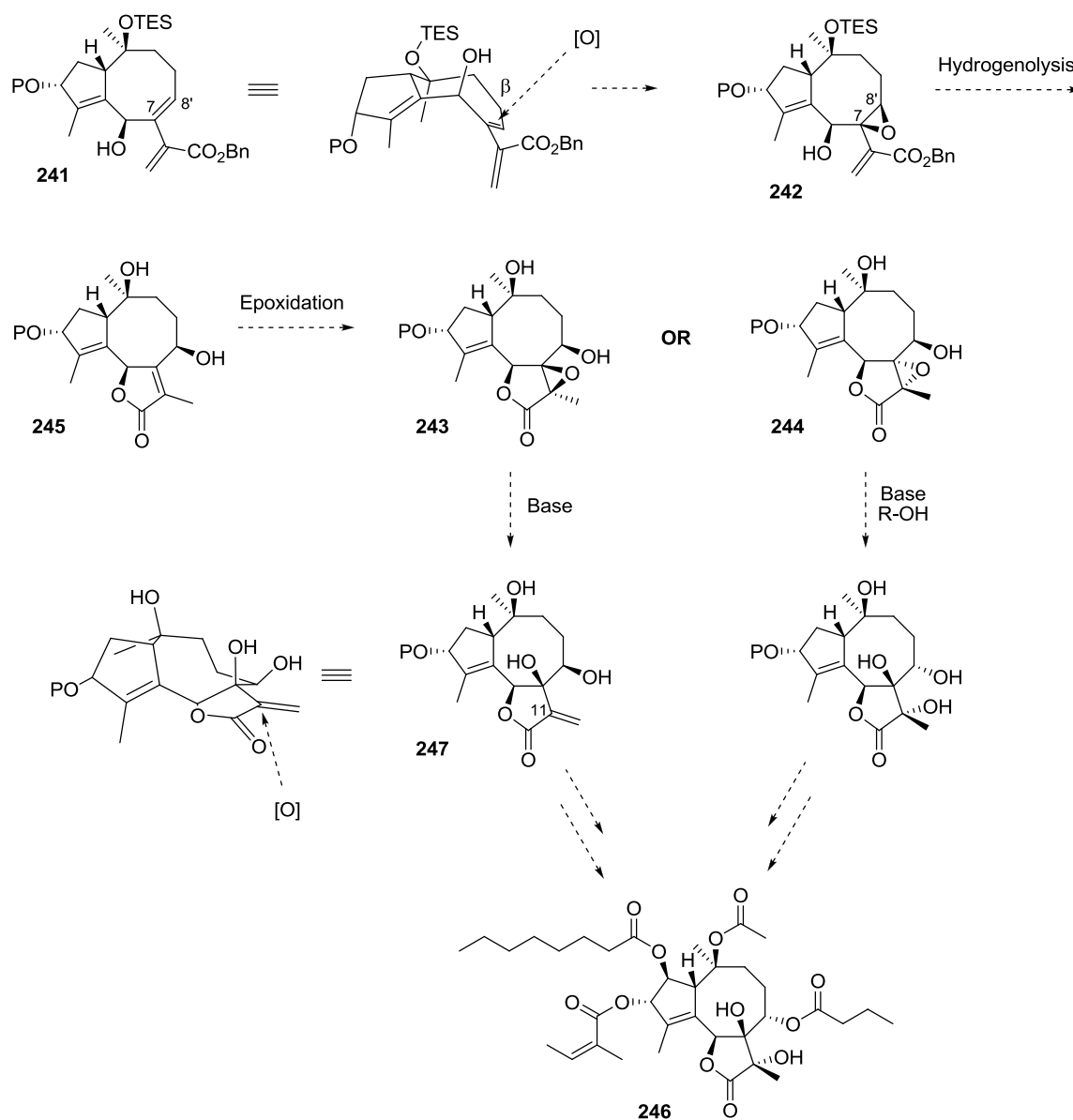
The scope of the synthetic strategy towards Tg **1** has also been expanded to include unnatural core-modified [5,8]-bicyclic analogue **230**, with the successful formation of the 8-membered carbocycle serving as proof of the versatility of the key ring-closing ene-yne metathesis reaction in our synthetic approach (Scheme 127). The configuration at the C-10 stereogenic centre still needs to be established.



Scheme 127. Synthesis of an unnatural [5,8]-bicyclic core.

By analogy to the natural [5,7]-bicyclic homologues, the 8-membered allylic alcohol **241** is predicted to exhibit facial selectivity during C-7/8 oxidation to epoxyalcohol **242** because reaction at the convex β -face is thought to minimise transannular strain (Scheme 128). Following the previously suggested strategy towards natural Tg **1**, epoxyalcohol **242** could

be converted into either of two epoxylactones **243** and **244** from unsaturated lactone **245** *via* hydrogenolysis, and then hopefully taken to [5,8,5] thapsigargin homologue **246**. Like methylene lactone **238**, compound **247** is predicted to allow access to the correct face for hydration across the C-11/13 olefin.



Scheme 128. Envisaged development towards a [5,8,5] thapsigargin homologue.

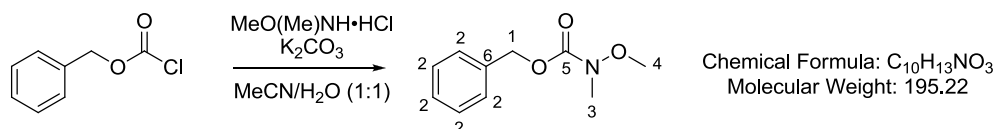
Experimental

General experimental

Nuclear magnetic resonance spectra were recorded on a Bruker DPX-400 spectrometer and a Bruker DPX-500 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-*d*, 7.26 ppm for ^1H NMR; chloroform-*d*, 77.0 ppm for ^{13}C NMR. Coupling constants (*J*) are quoted in Hertz. Carbon numbering system is used according to the structure of thapsigargin. High resolution mass spectra were recorded under FAB and CI conditions by the University of Glasgow analytical service. IR spectra were recorded using a Golden Gate TM attachment, utilizing a type IIa diamond as a single reflection element. Thin layer chromatography was performed on aluminium-backed plates coated with Merck Silica gel 60 F₂₅₄. The plates were developed using ultraviolet light, ethanolic anisaldehyde, ceric ammonium molybdate or KMnO₄. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was Merck KGaA Guduran silica gel 60. CH₂Cl₂, Toluene, and THF were all purified using Innovative Technology Solvent Purification System; Ac₂O was distilled from quinoline under reduced pressure; all other solvents and reagents were used as received from commercial suppliers unless stated otherwise. Air or moisture sensitive reactions were carried out in pre-dried glassware; either overnight in an oven (130 °C) or by flame drying *in vacuo*. Argon was used to create an inert atmosphere.

Experimental procedures

Benzyl methoxy(methyl)carbamate (**88**)



To a solution of MeO(Me)NH·HCl (1.00 g, 10.3 mmol) in acetonitrile (20 mL) was added a saturated aqueous solution of K₂CO₃ (20 mL) and benzyl chloroformate (1.46 mL, 10.3 mmol, 1 equiv) at room temperature. The mixture was stirred at the same temperature for 18 h. The reaction mixture was extracted with CH₂Cl₂ (x3) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 90:10) to give **88** as a colourless oil (2.00 g, 99%).

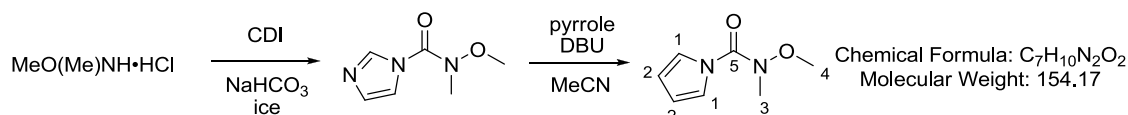
¹H NMR (400 MHz, CDCl₃): δ 7.42-7.29 (m, 5H, H-2), 5.19 (s, 2H, H-1), 3.70 (s, 3H, H-4), 3.17 (s, 3H, H-3) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 157.1 (C-5), 136.2 (C-6), 128.6 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 67.6 (C-1), 61.7 (C-4), 35.7 (C-3) ppm.

IR (thin film): 2935, 1703, 1456, 1411, 1388, 1340, 1153, 1045 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₀H₁₃NO₃ (M + Na)⁺ 218.0788, found 218.0785.

N-Methoxy-*N*-methyl-1*H*-pyrrole-1-carboxamide (**87**)



Ref: *Angew. Chemie Int. Ed.* **2015**, 54, 9839.

To a saturated aqueous solution of NaHCO₃ (100 mL) was added ice (100 g) and solid MeO(Me)NH·HCl (20.0 g, 205 mmol) portionwise at 0 °C. Then solid *N,N'*-carbonyldiimidazole (43.2 g, 267 mmol, 1.3 equiv) was added portionwise over the course

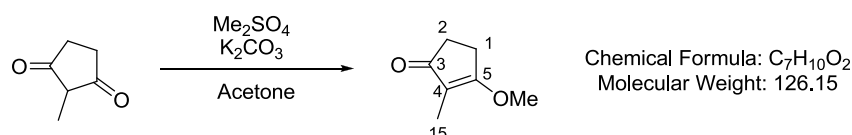
of 15 min and the mixture was left to stir at the same temperature for 30 min. The reaction mixture was then extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude product as a yellow oil (26.7 g). The residue was redissolved in dry acetonitrile (400 mL) and pyrrole (12.5 mL, 180 mmol, 1.05 equiv) was added dropwise at room temperature. Then DBU (25.7 mL, 172 mmol, 1 equiv) was added dropwise and stirring maintained for 3 h, after which the solvent was removed *in vacuo* and the residue partitioned between 1M HCl and EtOAc and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 90:10) to give **87** as a colourless oil (19.9 g, 63% over 2 steps).

^1H NMR (400 MHz, CDCl_3): δ 7.40 (dd, 2H, $J = 5.1, 2.8$ Hz, H-1), 6.25 (dd, 2H, $J = 5.1, 2.8$ Hz, H-2), 3.66 (s, 3H, H-4), 3.35 (s, 3H, H-3) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 152.2 (C-5), 121.4 (C-2), 111.3 (C-1), 60.9 (C-4), 35.3 (C-3) ppm.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2$ ($\text{M} + \text{Na}$) $^+$ 177.0639, found 177.0641.

3-Methoxy-2-methylcyclopent-2-enone (**78**)



Ref: *Eur. J. Org. Chem.* **2017**, 23, 3362-3372.

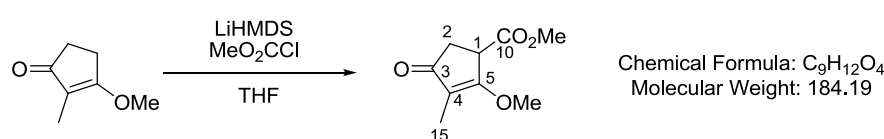
To a solution of dione **77** (10.0 g, 89.2 mmol) in dry acetone (100 mL) was added K_2CO_3 (13.6 g, 98.1 mmol, 1.1 equiv) and Me_2SO_4 (10.2 mL, 107 mmol, 1.2 equiv) at room temperature. The mixture was heated to reflux and stirred for 4 h, after which the reaction was cooled to rt, quenched with saturated aqueous NaHCO_3 and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give **78** as a yellow oil (11.2 g, 99%). The crude product was used for the next step without purification.

^1H NMR (400 MHz, CDCl_3): δ 3.96 (s, 3H, OMe), 2.65 (m, 2H, H-2a), 2.45 (m, 2H, H-2b), 1.64 (t, 3H, J = 1.7 Hz, H-15) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 205.3 (C-3), 184.4 (C-5), 116.2 (C-4), 56.4 (OMe), 33.4 (C-2), 24.7 (C-3), 6.0 (C-15) ppm.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_{10}\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 127.0759, found 127.0756.

Methyl 2-methoxy-3-methyl-4-oxocyclopent-2-enecarboxylate (**79**)



To a solution of HMDS (21.6 mL, 103 mmol, 1.3 equiv) in dry THF (500 mL) at 0 °C was added dropwise a solution of $n\text{BuLi}$ (41.2 mL, 103 mmol, 1.3 equiv, 2.5 M in hexanes). After stirring for 5 min, the temperature was lowered to -78 °C and cyclopentenone **78** (10.00 g, 79.2 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h, after which methylchloroformate (6.42 mL, 83.1 mmol, 1.05 equiv) was added slowly dropwise over the course of 5 min. The reaction was stirred for 1 h, then warmed up to 0 °C, quenched with saturated aqueous NaHCO_3 and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 80:20 up to 60:40) to give **79** as a yellow oil (12.5 g, 86%).

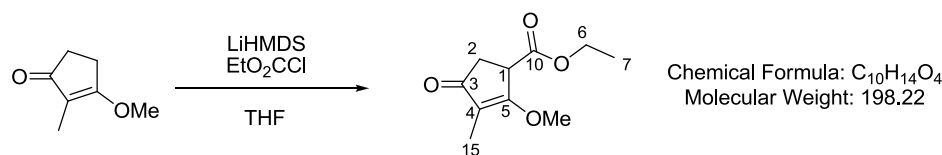
^1H NMR (400 MHz, CDCl_3): δ 4.02 (3H, s, COOMe), 3.76 (s, 3H, OMe), 3.71-3.75 (m, 1H, H-1), 2.71 (dd, 1H, J = 17.9, 7.7 Hz, H-2a), 2.55 (dd, 1H, J = 17.9, 2.5 Hz, H-2b), 2.25 (d, 3H, J = 0.9 Hz, H-15) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 203.0 (C-3), 179.1 (C-10), 171.6 (C-5), 116.6 (C-4), 58.0 (OMe), 52.5 (COOMe), 43.9 (C-1), 38.3 (C-2), 7.1 (C-15) ppm.

IR (thin film): 2967, 1735, 1692, 1471, 1375, 1342, 1240, 1160 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{12}\text{O}_4$ ($\text{M} + \text{Na}^+$) 207.0628, found 207.0626.

Ethyl 2-methoxy-3-methyl-4-oxocyclopent-2-enecarboxylate (90a)



To a solution of HMDS (1.66 mL, 7.92 mmol, 1 equiv) in dry THF (5 mL) at 0 °C was added dropwise a solution of $n\text{BuLi}$ (3.17 mL, 7.92 mmol, 1 equiv, 2.5 M in hexanes) and stirred for 5 min. The solution was transferred *via* cannula to a solution of cyclopentenone **78** (1.00 g, 7.92 mmol) in dry THF (50 mL) at -78 °C. The reaction mixture was stirred at the same temperature for 1 h, after which ethylchloroformate (0.790 mL, 8.32 mmol, 1.05 equiv) was added slowly dropwise over the course of 5 min. The reaction was stirred for 1 h, then warmed up to 0 °C, quenched with saturated aqueous NaHCO_3 and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 80:20 up to 60:40) to give **90a** as a yellow oil (1.05g, 67%).

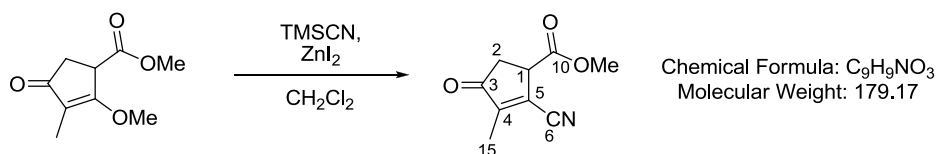
^1H NMR (400 MHz, CDCl_3): δ 4.21 (q, 2H, $J = 7.1$ Hz, H-6), 4.01 (s, 3H, OMe), 3.74 – 3.69 (m, 1H, H-1), 2.70 (dd, 1H, $J = 17.9, 7.7$ Hz, H-2a), 2.54 (dd, 1H, $J = 17.9, 2.6$ Hz, H-2b), 1.79 (d, 3H, $J = 1.4$ Hz, H-15), 1.27 (t, 3H, $J = 7.1$ Hz, H-7) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 203.3 (C-3), 179.4 (C-10), 171.4 (C-5), 116.9 (C-4), 61.7 (C-6), 58.0 (OMe), 44.1 (C-1), 38.5 (C-2), 14.1 (C-6), 7.2 (C-15) ppm.

IR (thin film): 2978, 1728, 1697, 1627, 1458, 1381, 1327, 1249, 1165 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{10}\text{H}_{14}\text{O}_4$ ($\text{M} + \text{Na}^+$) 221.0784, found 221.0782

Methyl 2-cyano-3-methyl-4-oxocyclopent-2-enecarboxylate (**81**)



ZnI₂ (1.38 g, 4.33 mmol, 0.1 equiv) was dried under vacuum for 4 h, after which ketoester **79** (7.97 g, 43.3 mmol) in dry CH₂Cl₂ (25 mL) was added. TMSCN (5.98 mL, 47.6 mmol, 1.1 equiv) was added dropwise and the solution was stirred for 24 h at rt, after which the solution was concentrated *in vacuo* using a trap filled with a NaClO/KOH solution. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 80:20) to give **81** as a yellow oil (5.25 g, 68%).

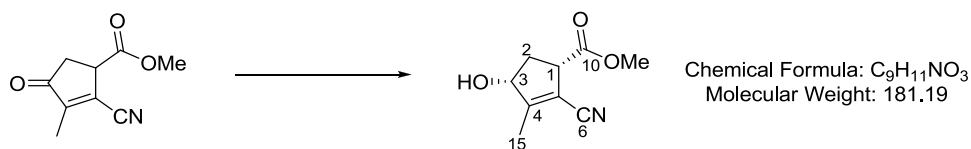
¹H NMR (400 MHz, CDCl₃): δ 3.93–3.87 (m, 1H, H-1), 3.84 (s, 3H, OCH₃), 2.87 (dd, 1H, *J* = 19.3, 2.9 Hz, H-2a), 2.76 (dd, 1H, *J* = 19.3, 7.4 Hz, H-2b), 2.05 (d, 3H, *J* = 2.2 Hz, H-15) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 203.5 (C-3), 169.7 (C-10), 154.7 (C-4), 133.3 (C-5), 114.0 (C-6), 53.3 (COOMe), 44.5 (C-2), 37.1 (C-1), 10.6 (C-15) ppm.

IR (thin film): 2956, 2836, 2223, 1738, 1647, 1436, 1343, 1338, 1244, 1162 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₉H₉NO₃ (M + Na)⁺ 202.0480, found 202.0471.

(1*S**,4*R**)-Methyl 2-cyano-4-hydroxy-3-methylcyclopent-2-enecarboxylate (**82**)



Method 1:

To a solution of ketoester **81** (6.65 g, 37.1 mmol) in dry methanol (120 mL) at -78 °C was added solid NaBH₄ (1.42 g, 37.5 mmol, 1.01 equiv) portion-wise. The mixture was left to stir at -78 °C for 2 h, followed by the addition of brine at -78 °C. After 30 min the temperature was raised to rt and stirring continued for a further 30 min. The mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine,

dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 60:40) to give **82** as a colourless oil (6.16 g, 92%, dr 4:1).

Method 2:

To a solution of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (414 mg, 0.677 mmol, 0.01 equiv) in CH_2Cl_2 (340 mL, distilled from CaH_2) was added (*R,R*)-TsDPEN (494 mg, 1.35 mmol, 0.02 equiv) and the mixture was left to stir for 3 h at rt. Ketoester **81** (12.1 g, 67.7 mmol) was then added followed by a mixture of $\text{Et}_3\text{N}/\text{HCOOH}$ (2:5, 11.52 mL). The temperature was raised to 30 °C and the reaction was stirred for 18 h. Aqueous HCl (1 M) was added and the two layers separated. The organic layer was washed with further 1 M aqueous HCl (x2), saturated aqueous NaHCO_3 and brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 60:40) to give **82** as a colourless oil (9.93 g, 81%, dr 9:1, 98.9% ee).

Chiral HPLC: Chiralpak AD-H, hexane/*i*PrOH 88:12, $T = 25^\circ\text{C}$, $\lambda = 214\text{ nm}$, retention time: *trans*-**82** 10.573 min and 11.682 min; *cis*-**82** 12.448 min and 14.031 min. HPLC traces are included in Appendix C.

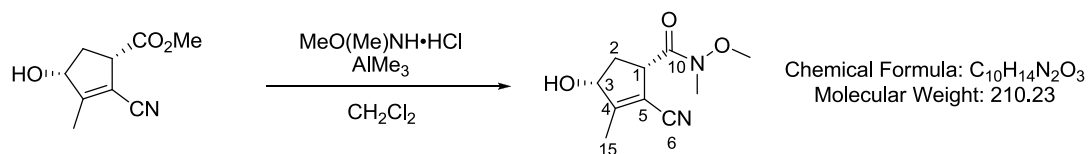
^1H NMR (400 MHz, CDCl_3): δ 4.56 (ddd, 1H, $J = 10.5, 7.3, 2.3\text{ Hz}$, H-3), 3.81 (s, 3H, OCH_3), 3.62 (dtd, 1H, $J = 6.5, 4.3, 1.8\text{ Hz}$, H-1), 2.74 (d, 1H, $J = 10.5\text{ Hz}$, OH), 2.46 (ddd, 1H, $J = 14.5, 7.9, 7.3\text{ Hz}$, H-2a), 2.12 (dd, 3H, $J = 1.8, 0.7\text{ Hz}$, H-15), 2.10-2.04 (m, 1H, H-2b) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 174.1 (C-10), 164.1 (C-4), 114.8 (C-6), 109.7 (C-5), 78.0 (C-3), 53.1 (COOMe), 49.6 (C-2), 36.4 (C-1), 14.3 (C-15) ppm.

IR (thin film): 3456, 2959, 2225, 1735, 1646, 1433, 1380, 1341, 1206, 1050 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{11}\text{NO}_3$ ($\text{M} + \text{Na}$) $^+$ 204.0637, found 204.0630.

(1*R*,4*S*)-2-Cyano-4-hydroxy-*N*-methoxy-*N*,3-dimethylcyclopent-2-enecarboxamide
(83)



To a solution of MeONHMe.HCl (9.62 g, 98.6 mmol, 1.8 equiv) in dry CH₂Cl₂ (300 mL) at 0 °C was added dropwise a solution of AlMe₃ (32.9 mL, 98.6 mmol, 1.8 equiv, 3.0 M in toluene). The mixture was stirred for 1 h, after which a solution of **82** (9.93 g, 54.8 mmol, dr 9:1) in dry CH₂Cl₂ (25 mL) was added dropwise at 0 °C. The mixture was allowed to warm up to rt and left to stir for 18 h. The reaction was quenched with saturated aqueous Rochelle's salt and the aqueous phase was extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 70:30 up to 50:50) to give **83** as a yellow oil (10.6 g, 92%, dr 27:1)

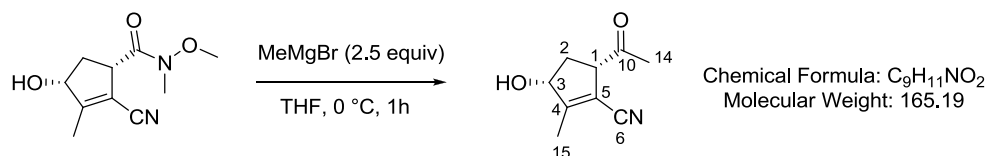
¹H NMR (400 MHz, CDCl₃): δ 4.47 (dd, 1H, *J* = 11.5, 7.8 Hz, H-3), 4.25 (d, 1H, *J* = 7.8 Hz, OH), 4.15 (d, 1H, *J* = 11.5 Hz, H-1), 3.84 (s, 3H, OCH₃), 3.27 (s, 3H, NCH₃), 2.34–2.26 (m, 1H, H-2a), 2.13 (d, 3H, *J* = 1.2 Hz, H-15), 1.97 (d, 1H, *J* = 14.2 Hz, H-2b) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 173.3 (C-10), 164.9 (C-4), 115.6 (C-5), 109.6 (C-6), 77.9 (C-3), 62.2 (OMe), 46.2 (C-2), 36.9 (C-1), 32.55 (NMe), 14.5 (C-15) ppm.

IR (thin film): 3426, 2943, 2217, 1641, 1438, 1390, 1175, 1080, 1045, 1001 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₀H₁₄N₂O₃ (M + Na)⁺ 233.0902, found 233.0896.

[α]_D²⁵ -238.1 (*c* 1.0, CHCl₃)

(3R,5S)-5-Acetyl-3-hydroxy-2-methylcyclopent-1-enecarbonitrile (84)

To a solution of amide **83** (5.32 g, 25.3 mmol) in dry THF (20 mL) at 0 °C was added dropwise a solution of MeMgBr (21.1 mL, 63.3 mmol, 2.5 equiv, 3.0 M in Et₂O). The reaction was stirred for 1 h at 0 °C, after which it was quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude yellow oil **84** (4.18 g) was used without further purification. A small sample was taken and recrystallised *via* slow vapour diffusion of hexane into EtOAc.

m.p. : 94-96 °C

¹H NMR (400 MHz, CDCl₃): δ 4.55-4.47 (m, 1H), 3.87-3.80 (m, 1H), 2.88 (d, 1H, *J* = 10.6 Hz), 2.41 (s, 3H), 2.39-2.31 (m, 1H), 2.11-2.08 (m, 3H), 1.96 (dt, 1H, *J* = 14.3, 2.2 Hz) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 208.6 (C-10), 164.2 (C-4), 115.2 (C-6), 109.4 (C-5), 77.8 (C-3), 57.1 (C-1), 35.8 (C-2), 30.4 (C-14), 14.4 (C-15) ppm.

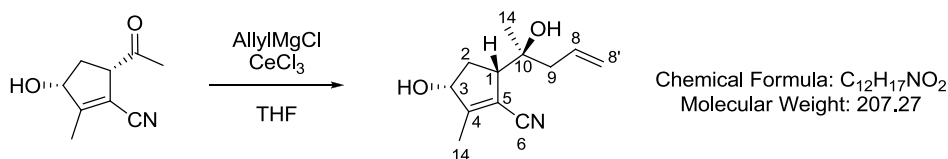
IR (thin film): 3432, 2220, 1706, 1640, 1438, 1362, 1176, 1085, 1039 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₉H₁₁NO₂ (M + Na)⁺ 188.0687, found 188.0683.

[α]_D²⁵ -157.1 (*c* 1.0, CHCl₃)

X-ray data is included in Appendix A.

(3R,5S)-3-Hydroxy-5-((S)-2-hydroxypent-4-en-2-yl)-2-methylcyclopent-1-enecarbonitrile (103)



CeCl₃·7H₂O (22.7g, 60.9 mmol, 2.2 equiv) was dried under vacuum at 60 °C (4 h), 80 °C (4 h), 120 °C (12 h), 140 °C (4 h), in that order. Dry THF (275 mL) was added and the white suspension was sonicated at rt for 1 h. The suspension was then cooled to -78 °C and allylmagnesium chloride (30.5 mL, 60.9 mmol, 2.2 equiv, 2 M in THF) was added dropwise. The solution was stirred for 1 h at the same temperature, after which a solution of ketone **84** (4.57 g, 27.7 mmol) in dry THF (25 mL) was added dropwise and left to stir for 2 h. The reaction was quenched with saturated aqueous NH₄Cl and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 60:40 up to 40:60) to give **103** as a colourless oil (5.31 g, 93% over 2 steps, dr 6:1). Major isomer signals reported.

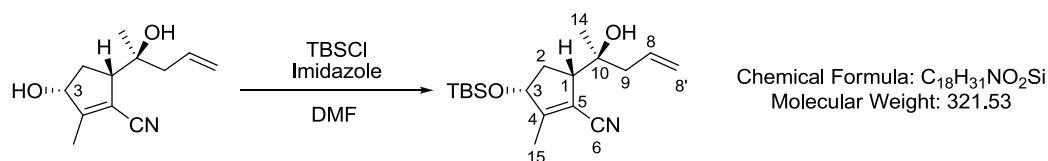
¹H NMR (400 MHz, CDCl₃): δ 5.91-5.78 (m, 1H, H-8), 5.28-5.13 (m, 2H, H-8'), 4.41-4.30 (m, 1H, H-3), 3.47 (d, 1H, *J* = 10.8 Hz, OH), 2.88-2.82 (m, 1H, H-1), 2.37-2.21 (m, 3H, H-2a + H-9), 2.13-2.08 (m, 3H, H-15), 1.99-1.89 (m, 1H, H-2b), 1.45 (s, 3H, H-14) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 164.3 (C-4), 132.6 (C-8), 120.3 (C-8'), 117.5 (C-6), 111.1 (C-5), 76.9 (C-3), 72.6 (C-10), 53.9 (C-9), 46.2 (C-1), 34.9 (C-2), 25.8 (C-14), 14.6 (C-15) ppm.

IR (thin film): 3435, 2221, 1707, 1642, 1439, 1364, 1177, 1087, 1040 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₂H₁₇NO₂ (M + Na)⁺ 230.1157, found 230.1153.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-((*S*)-2-hydroxypent-4-en-2-yl)-2-methylcyclopent-1-carbonitrile (125**)**



To a solution of diol **103** (5.31 mg, 25.6 mmol) in dry DMF (40 mL) was added imidazole (6.95 g, 102 mmol, 4 equiv) and TBDMSCl (7.72 g, 51.2 mmol, 2 equiv). The reaction was heated to 40 °C and stirred for 18 h. The reaction was quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1 up to 95:5) to give **125** as a colourless oil and a single diastereomer (6.87 g, 83%), and minor diastereomer **125a** in variable yields.

¹H NMR (400 MHz, CDCl₃): δ 5.88 (ddt app, 1H, *J* = 17.8, 10.3, 7.5 Hz, H-8), 5.22-5.13 (m, 2H, H-8'), 4.56-4.50 (m, 1H, H-3), 2.95-2.87 (m, 1H, H-1), 2.38-2.26 (m, 3H, H-2a + H-9), 2.01 (dd, 3H, *J* = 2.1, 0.9 Hz, H-15), 1.69 (ddd, 1H, *J* = 13.7, 5.7, 4.7 Hz, H-2b), 1.21 (s, 3H, H-14), 0.90 (s, 9H, CH₃-TBS), 0.11 (s, 3H, CH₃-TBS), 0.11 (s, 3H, CH₃-TBS) ppm.

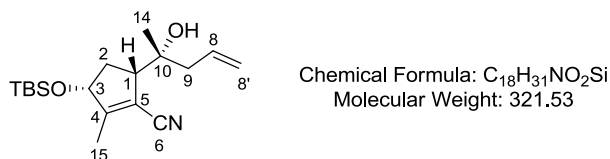
¹³C NMR (101 MHz, CDCl₃): δ 163.4 (C-6), 133.3 (C-8), 119.5 (C-8'), 117.2 (C-6), 111.3 (C-5), 77.3 (C-3), 72.7 (C-10), 53.6 (C-1), 44.9 (C-9), 35.6 (C-2), 25.7 (Me₃C-TBS), 25.0 (C-14), 18.0 (Me₃C-TBS), 14.4 (C-15), -4.6 (Me-TBS), -4.7 (Me-TBS) ppm.

IR (thin film): 3432, 3080, 2957, 2930, 2215, 1640, 1460, 1257, 1100 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₈H₃₁NO₂Si (M + Na)⁺ 344.2022, found 344.2020.

[α]_D²⁵ +3.0 (*c* 1.0, CHCl₃)

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-((*S*)-2-hydroxypent-4-en-2-yl)-2-methylcyclopent-1-carbonitrile (125a)



¹H NMR (400 MHz, CDCl₃): δ 5.90 (ddt app, 1H, *J* = 17.0, 10.5, 7.4 Hz, H-8), 5.25-5.10 (m, 2H, H-8'), 4.58-4.52 (m, 1H, H-3), 2.92-2.83 (m, 1H, H-1), 2.38-2.31 (m, 1H, H-2a), 2.38-2.23 (m, 2H, H-9), 1.99 (dd, 3H, *J* = 2.1, 1.0 Hz, H-15), 1.50 (ddd, 1H, *J* = 13.2, 6.7, 5.6 Hz, H-2b), 1.20 (s, 3H, H-14), 0.90 (s, 9H, CH₃-TBS), 0.10 (s, 3H, CH₃-TBS), 0.09 (s, 3H, CH₃-TBS) ppm.

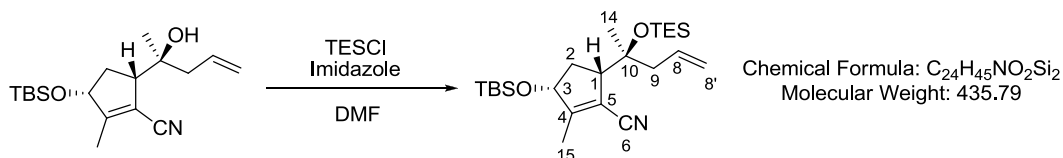
¹³C NMR (101 MHz, CDCl₃): δ 163.4 (C-6), 133.3 (C-8), 119.5 (C-8'), 117.2 (C-6), 111.0 (C-5), 77.6 (C-3), 73.2 (C-10), 53.4 (C-1), 44.8 (C-9), 36.1 (C-2), 25.7 (Me₃C-TBS), 24.0 (C-14), 18.0 (Me₃C-TBS), 14.2 (C-15), -4.6 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 3471, 2931, 2854, 2214, 1643, 1465, 1257, 1096, 833 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₈H₃₁NO₂Si (M + Na)⁺ 344.2022, found 344.2019.

[α]_D²⁵ -0.75 (*c* 1.0, CHCl₃)

(3*R,5*S**)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-((*S*)-2-triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enecarbonitrile (104)**



To a solution of alcohol **125** (5.90 g, 18.4 mmol) in dry DMF (30 mL) was added imidazole (12.5 g, 184 mmol, 10 equiv) and TESCO (15.4 mL, 91.8 mmol, 5 equiv). The reaction was heated to 80 °C and stirred for 24 h. The reaction was quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with 1 M aqueous HCl, brine (x4), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column

chromatography (petroleum ether/ethyl acetate, 99:1) to give **104** as a colourless oil (7.84 g, 98%).

¹H NMR (400 MHz, CDCl₃): δ 5.86 (ddt app, 1H, *J* = 17.7, 10.4, 7.3 Hz, H-8), 5.15-5.07 (m, 2H, H-8'), 4.55-4.50 (m, 1H, H-3), 2.88-2.80 (m, 1H, H-1), 2.43-2.21 (m, 3H, H-2a + H-9), 1.95 (dd, 3H, *J* = 2.3, 1.2 Hz, H-15), 1.63 (ddd, 1H, *J* = 13.1, 7.8, 6.8 Hz, H-2b), 1.31 (s, 3H, H-14), 0.95 (t, 9H, *J* = 7.9 Hz, CH₃-TBS) 0.90 (s, 9H, CH₃-TES), 0.66-0.58 (m, 6H, CH₂-TES), 0.09 (s, 3H, CH₃-TBS), 0.08 (s, 3H, CH₃-TBS) ppm.

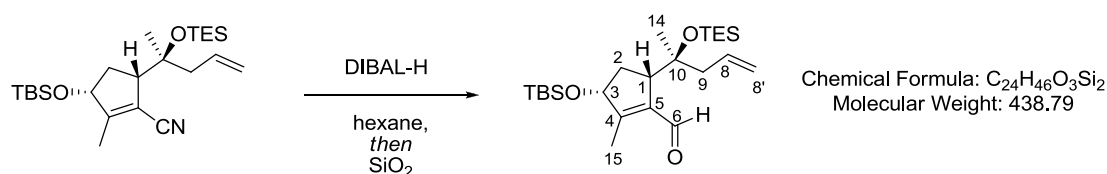
¹³C NMR (101 MHz, CDCl₃): δ 164.0 (C-6), 134.3 (C-8), 118.1 (C-8'), 117.4 (C-6), 110.7 (C-5), 77.5 (C-3), 76.0 (C-10), 53.2 (C-1), 45.4 (C-9), 35.9 (C-2), 25.7 (Me₃C-TBS), 25.5 (C-14), 18.0 (Me₃C-TBS), 14.1 (C-15), 7.1 (CH₂-TES), 6.8 (CH₃-TES), -4.5 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (cm⁻¹): 2950, 2881, 1640, 1460, 1340, 1250, 1058, 1002, 903.

HRMS (ESI): *m/z* calculated for C₂₄H₄₅NO₂Si₂ (M + Na)⁺ 458.2887, found 458.2869.

[α]_D²⁵ -5.6 (*c* 1.0, CHCl₃)

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-((*S*)-2-triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enecarbaldehyde (105**)**



To a solution of nitrile **104** (1.00 g, 2.29 mmol) in dry hexane at -78 °C was added dropwise a solution of DIBAL-H (3.44 mL, 3.44 mmol, 1.5 equiv, 1 M in hexane). The mixture was warmed to 0 °C for 20 min then cooled back down to -78 °C. Ethyl acetate (5 mL) was added to quench the excess DIBAL-H and the reaction mixture was left to stir for 10 min, after which SiO₂ (10g) was added and the temperature raised to rt and stirring maintained for a further 4 h. The reaction was filtered and concentrated *in vacuo* to give crude aldehyde **105** as a colourless oil (1.01g, 100%). The residue was taken on into the next reaction without further purification.

^1H NMR (400 MHz, CDCl_3): δ 9.91 (s, 1H, H-6), 5.86 (dddd, 1H, $J = 17.0, 10.3, 7.6, 6.8$ Hz, H-8), 5.07-4.98 (m, 2H, H-8'), 4.49-4.43 (m, 1H, H-3), 3.13-3.06 (m, 1H, H-1), 2.37-2.12 (m, 3H, H-2a + H-9), 2.01 (dd, 3H, $J = 2.0, 1.0$ Hz, H-15), 1.57-1.47 (m, 1H, H-2b), 1.19 (s, 3H, H-14), 0.94 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$) 0.91 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.64-0.56 (m, 6H, $\text{CH}_2\text{-TES}$), 0.10 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.09 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

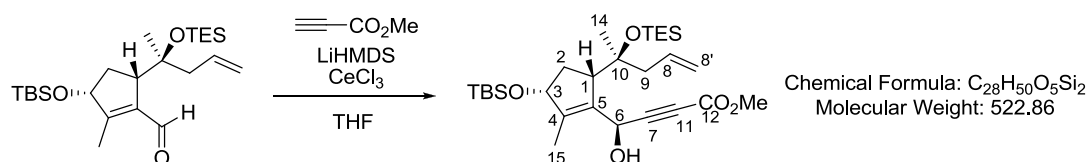
^{13}C NMR (101 MHz, CDCl_3): δ 192.8 (C-6), 157.5 (C-4), 137.4 (C-5), 135.0 (C-8), 117.4 (C-8'), 78.5 (C-3), 77.6 (C-10), 53.7 (C-9), 44.2 (C-1), 35.3 (C-2), 26.3 (C-14), 25.8 ($\text{Me}_3\text{C-TBS}$), 18.1 ($\text{Me}_3\text{C-TBS}$), 13.0 (C-14), 7.2 ($\text{CH}_2\text{-TES}$), 7.0 ($\text{CH}_3\text{-TES}$), -4.5 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2942, 2885, 1680, 1632, 1456, 1360, 1231, 1128, 1068, 1012 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{46}\text{O}_3\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 461.2883, found 461.2863.

$[\alpha]_{\text{D}}^{25}$ -43.3 (c 1.0, CHCl_3)

(*R*)-Methyl 4-((3*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-((*S*)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)-4-hydroxybut-2-ynoate (128)



$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2.56 g, 6.88 mmol, 3 equiv) was dried under vacuum at 60 $^\circ\text{C}$ (4 h), 80 $^\circ\text{C}$ (4 h), 100 $^\circ\text{C}$ (12 h), 140 $^\circ\text{C}$ (4 h), in that order. Dry THF (50 mL) was added and the white suspension was sonicated for 1 h then cooled to -78 $^\circ\text{C}$. To a separate solution of HMDS (1.44 mL, 6.88 mmol, 3 equiv) in dry THF (5 mL) at 0 $^\circ\text{C}$ was added dropwise a solution of $n\text{BuLi}$ (2.75 mL, 6.88 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to the reaction mixture. Methyl propiolate (0.61 mL, 6.88 mmol, 3 equiv) was added dropwise and after stirring at -78 $^\circ\text{C}$ for 10 min, aldehyde **105** (1.01 g, 2.29 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 $^\circ\text{C}$ for 1 h. The reaction was quenched with saturated aqueous NH_4Cl , diluted with brine and the aqueous phase was extracted with ethyl acetate (x3). The combined organic

layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **128** as a colourless oil (1.08 g, 90%).

^1H NMR (400 MHz, CDCl_3): δ 5.98-5.85 (m, 1H, H-8), 5.27 (d, 1H, $J = 9.1$ Hz, H-6), 5.10-5.02 (m, 2H, H-8'), 4.79 (d, 1H, $J = 9.1$ Hz, OH), 4.41 (dd, 1H, $J = 7.6, 4.1$ Hz, H-3), 3.76 (s, 3H, COOMe), 2.94 (t, 1H, $J = 6.1$ Hz, H-1), 2.52 (dd, 1H, $J = 14.4, 7.3$ Hz, H-2a), 2.45-2.25 (m, 2H, H-9), 1.76 (d, 3H, $J = 1.3$ Hz, H-15), 1.36-1.29 (m, 1H, H-2b), 1.26 (s, 3H, H-14), 0.98 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$) 0.89 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.75-0.66 (m, 6H, $\text{CH}_3\text{-TES}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.06 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

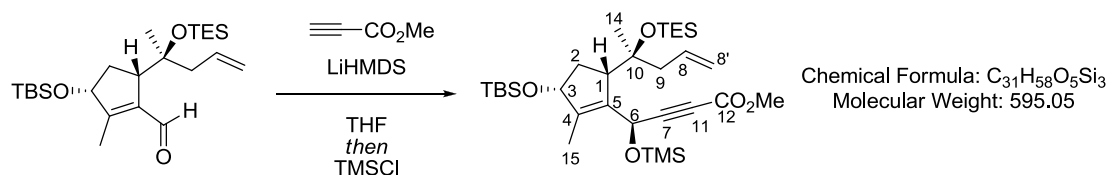
^{13}C NMR (101 MHz, CDCl_3): δ 154.0 (C-12), 142.7 (C-4), 135.2 (C-5), 134.9 (C-8), 117.9 (C-8'), 87.8 (C-7), 80.1 (C-11), 78.2 (C-3), 76.2 (C-10), 59.5 (COOMe), 57.4 (C-1), 52.6 (C-6), 42.1 (C-9), 36.5 (C-2), 26.3 (C-14), 25.8 ($\text{Me}_3\text{C-TBS}$), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.5 (C-15), 7.0 ($\text{CH}_2\text{-TES}$), 6.9 ($\text{CH}_3\text{-TES}$), -4.5 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 3396, 2954, 2875, 2222, 1703, 1360, 1257, 1160, 1058, 1002 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{28}\text{H}_{50}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 545.3094, found 545.3086.

$[\alpha]_{\text{D}}^{25}$ -22.0 (c 1.0, CHCl_3)

(*R)-Methyl 4-((3*R**,5*S**)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-((*S**)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)-4-hydroxybut-2-ynoate (129)**



To a solution of HMDS (71 μL , 0.34 mmol, 1.5 equiv) in dry THF (5 mL) at 0 $^\circ\text{C}$ was added dropwise a solution of $n\text{BuLi}$ (0.14 mL, 0.35 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to a solution of methyl propiolate (30 μL , 0.34 mmol, 1.5 equiv) in dry THF (5 mL) at -78 $^\circ\text{C}$. After stirring for 10 min, aldehyde **105** (100 mg, 0.23 mmol) in dry THF (2 mL) was added dropwise to the reaction mixture and stirred at -78 $^\circ\text{C}$ for 1 h. TMSCl (86 μL , 0.69 mmol, 3 equiv) was added dropwise and

reaction was allowed to warm up to room temperature and stirred for 18 h. The reaction was then quenched with saturated aqueous NaHCO_3 and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **129** as a colourless oil (136 mg, 100%).

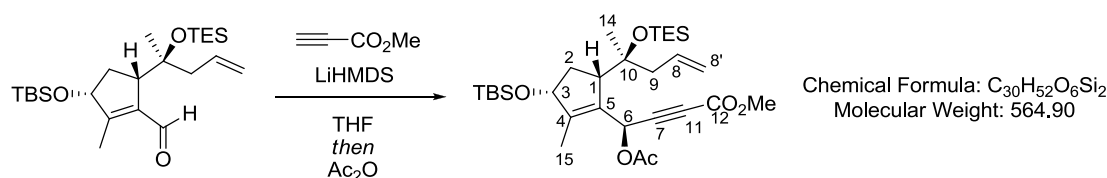
^1H NMR (400 MHz, CDCl_3): 5.91 (dddd, 1H, $J = 16.3, 10.2, 8.5, 6.0$ Hz, H-8), 5.82 (s, 1H, H-6), 5.07-4.97 (m, 2H, H-8'), 4.39 (t, 1H, $J = 6.7$ Hz, H-3), 3.75 (s, 3H, COOMe), 2.80-2.69 (m, 1H, H-1), 2.31-2.05 (m, 3H, H-9 + H-2a), 1.86 (d, 3H, $J = 1.5$ Hz, H-15), 1.24 (ddd, 1H, $J = 13.7, 7.7, 6.1$ Hz, H-2b), 1.15 (d, 3H $J = 11.0$ Hz, H-14), 0.98 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.90 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.66 (q, 6H, $J = 7.5$ Hz, $\text{CH}_2\text{-TES}$), 0.19 (s, 9H, $\text{CH}_3\text{-TMS}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.06 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 154.1 (C-12), 143.8 (C-4), 135.2 (C-5), 134.8 (C-8), 117.2 (C-8'), 88.9 (C-7), 78.8 (C-11), 78.4 (C-3), 75.8 (C-10), 60.3 (C-6), 55.3 (COOMe), 52.5 (C-1), 41.9 (C-9), 37.0 (C-2), 26.2 (C-14), 25.9 ($\text{Me}_3\text{C-TBS}$), 18.2 ($\text{Me}_3\text{C-TBS}$), 12.7 (C-15), 7.4 ($\text{CH}_2\text{-TES}$), 7.1 ($\text{CH}_3\text{-TES}$), 0.1 (Me-TMS), -4.4 (Me-TBS), -4.7 (Me-TBS) ppm.

IR (thin film): 2954, 2876, 2230, 1721, 1359, 1250, 1080, 840 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{31}\text{H}_{58}\text{O}_5\text{Si}_3$ ($\text{M} + \text{Na}$) $^+$ 617.3490, found 617.3462.

(*R)-Methyl 4-acetoxy-4-((3*R**,5*S**)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-((*S**)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)but-2-ynoate (**130**)**



To a solution of HMDS (270 μL , 1.29 mmol, 3 equiv) in dry THF (10 mL) at 0 $^\circ\text{C}$ was added dropwise a solution of $n\text{BuLi}$ (516 μL , 1.29 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to a solution of methyl propiolate (114 μL , 1.29 mmol, 3 equiv) in dry THF (10 mL) at -78 $^\circ\text{C}$. After stirring for 10 min, aldehyde **105** (188 mg, 0.430 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture

was stirred at -78 °C for 1 h. Ac₂O (243 µL, 2.57 mmol, 6 equiv) was added dropwise, the reaction was allowed to warm up to room temperature and stirred for 18 h. The reaction was then quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **130** as a colourless oil (179 mg, 74%).

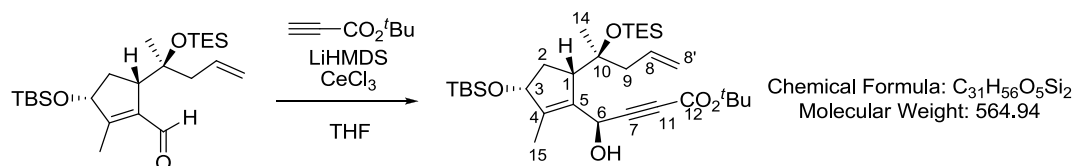
¹H NMR (500 MHz, CDCl₃): δ 6.73 (s, 1H, H-6), 5.88 (dddd, 1H, *J* = 16.8, 10.2, 8.1, 6.5 Hz, H-8), 5.06-4.95 (m, 2H, H-8'), 4.43 (dd, 1H, *J* = 7.2, 6.3 Hz, H-3), 3.75 (s, 3H, COOMe), 2.85-2.75 (m, 1H, H-1), 2.26 (dt app, 1H, *J* = 13.1, 7.9 Hz, H-2a), 2.17 (dd, 1H, *J* = 14.1, 6.5 Hz, H-9a), 2.11 (s, 3H, OAc), 2.10 – 2.06 (m, 1H, H-9b), 1.87 (dd, 3H, *J* = 2.0, 0.7 Hz, H-15), 1.28 (ddd, 1H, *J* = 10.0, 8.0, 4.2 Hz, H-2b), 1.17 (s, 3H, H-14), 0.97 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.91 (s, 9H, CH₃-TBS), 0.70-0.63 (m, 6H, CH₂-TES), 0.09 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 169.2 (Ac), 153.7 (C-12), 146.2 (C-5), 134.9 (C-5), 131.2 (C-8), 117.4 (C-8'), 84.5 (C-7), 78.5 (C-11), 78.1 (C-3), 76.3 (C-10), 60.6 (C-6), 55.8 (COOMe), 52.6 (C-1), 41.9 (C-9), 36.9 (C-2), 26.3 (C-14), 25.9 (Me₃C-TBS), 20.8 (Ac), 18.1 (Me₃C-TBS), 13.0 (C-15), 7.2 (CH₂-TES), 7.0 (CH₃-TES), -4.4 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 2955, 2877, 2237, 1720, 1249, 1219, 1064, 1002, 833 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₀H₅₂O₆Si₂ (M + Na)⁺ 587.3195, found 587.3172.

(*R)-tert-Butyl 4-((3*R**,5*S**)-3-(tert-butyldimethylsilyloxy)-2-methyl-5-((*S**)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)-4-hydroxybut-2-ynoate (131)**



CeCl₃·7H₂O (127 mg, 0.34 mmol, 3 equiv) was dried under vacuum at 60 °C (4 h), 80 °C (4 h), 100 °C (12 h), 140 °C (4 h), in that order. Dry THF (2 mL) was added and the white

suspension was sonicated for 1 h then cooled to -78 °C. To a separate solution of HMDS (71 µL, 0.34 mmol, 3 equiv) in dry THF (2 mL) at 0 °C was added dropwise a solution of ⁿBuLi (136 µL, 0.34 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to the reaction mixture. *tert*-Butyl propiolate (43.1 mg, 0.34 mmol, 3 equiv) was then added dropwise at -78 °C and after stirring for 10 min, aldehyde **105** (50 mg, 0.11 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. Saturated aqueous NH₄Cl was slowly added and the reaction was warmed to room temperature and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 97:3) to give **131** as a colourless oil (48 mg, 75%).

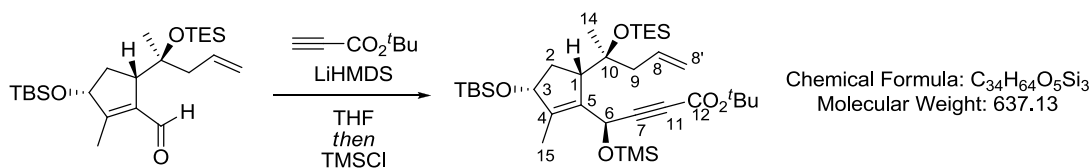
¹H NMR (500 MHz, CDCl₃): δ 5.91 (ddt app, 1H, *J* = 17.5, 10.2, 7.5 Hz, H-8), 5.23 (d, 1H, *J* = 9.3 Hz, H-6), 5.10-5.02 (m, 2H, H-8'), 4.74 (d, 1H, *J* = 9.3 Hz, OH), 4.40 (dd, 1H, *J* = 7.5, 4.5 Hz, H-3), 2.93 (t app, 1H, *J* = 6.2 Hz, H-1), 2.57 (dd, 1H, *J* = 14.5, 7.2 Hz, H-2a), 2.35 (dd, 1H, *J* = 14.5, 7.2 Hz, H-2b), 2.29 (dt app, 1H, *J* = 13.7, 8.4 Hz, H-9a), 1.75 (d, 3H, *J* = 1.3 Hz, H-15), 1.46 (s, 9H, COO^tBu), 1.34-1.28 (m, 1H, H-9b), 1.27 (s, 3H, H-14), 0.98 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.89 (s, 9H, CH₃-TBS), 0.70 (q, 6H, *J* = 7.9 Hz, CH₂-TES), 0.07 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 152.7 (C-12), 142.4 (C-4), 135.3 (C-5), 135.0 (C-8), 117.8 (C-8'), 84.9 (C-7), 83.0 (C-11), 80.1 (C-3), 78.2 (C-10), 77.8 (Me₃C-^tBu), 59.5 (C-1), 57.4 (C-6), 42.0 (C-9), 36.5 (C-2), 28.0 (Me₃C-^tBu), 26.3 (C-14), 25.8 (Me₃C-TBS), 18.1 (Me₃C-TBS), 12.4 (C-15), 7.1 (CH₂-TES), 6.9 (CH₃-TES), -4.5 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (cm⁻¹): 2954, 2877, 2222, 1705, 1257, 1157, 1056, 1002, 840.

HRMS (ESI): *m/z* calculated for C₃₁H₅₆O₅Si₂ (M + Na)⁺ 587.3558, found 587.3532.

(*R)-tert-Butyl 4-((3*R**,5*S**)-3-(tert-butyldimethylsilyloxy)-2-methyl-5-((*S**)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)-4-(trimethylsilyloxy)but-2-ynoate (132)**



To a solution of HMDS (193 μ L, 0.92 mmol, 3 equiv) in dry THF (5 mL) at 0 °C was added dropwise a solution of *n*BuLi (368 μ L, 0.92 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to a solution of *tert*-butyl propiolate (116 mg, 0.920 mmol, 3 equiv) in dry THF (5 mL) at -78 °C. After stirring for 10 min, aldehyde **105** (135 mg, 0.310 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. TMSCl (389 μ L, 3.08 mmol, 10 equiv) was added dropwise and reaction was allowed to warm up to room temperature and stirred for 18 h. The reaction was then quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **132** as a colourless oil (62 mg, 32%).

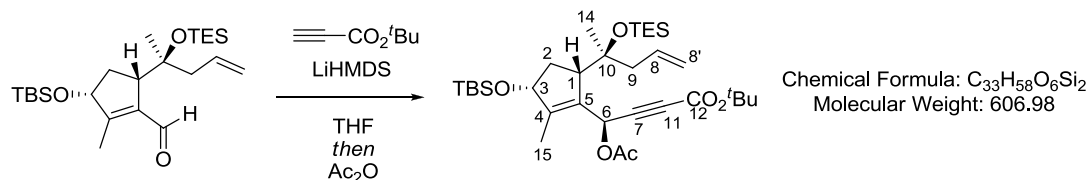
¹H NMR (400 MHz, CDCl₃): δ 5.97-5.86 (m, 1H, H-8), 5.78 (s, 1H, H-6), 5.08-4.98 (m, 2H, H-8'), 4.39 (t app, 1H, *J* = 6.7 Hz, H-3), 2.75 (t app, 1H, *J* = 7.8 Hz, H-1), 2.30-2.17 (m, 2H, H-9), 2.12 (dd, 1H, *J* = 14.2, 8.4 Hz, H-2a), 1.86 (d, 3H, *J* = 1.3 Hz, H-15), 1.47 (s, 9H, COO^{*t*}Bu), 1.29-1.20 (m, 1H, H-2b), 1.16 (s, 3H, H-14), 0.98 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.90 (s, 9H, CH₃-TBS), 0.67 (q, 6H, *J* = 7.7 Hz, CH₂-TES), 0.19 (s, 9H, CH₃-TMS), 0.08 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 153.6 (C-12), 144.0 (C-4), 136.0 (C-5), 135.8 (C-8), 117.9 (C-8'), 86.7 (C-7), 83.6 (C-11), 79.6 (C-3), 79.1 (C-10), 78.2 (Me₃C-^{*t*}Bu), 61.3 (C-1), 56.1 (C-6), 42.7 (C-9), 37.7 (C-2), 28.8 (Me₃C-^{*t*}Bu), 27.0 (C-14), 26.7 (Me₃C-TBS), 19.0 (Me₃C-TBS), 13.5 (C-15), 8.1 (CH₂-TES), 7.8 (CH₃-TES), 0.0 (Me-TMS), -4.5 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 2968, 2950, 2234, 1720, 1660, 1472, 1432, 1375, 1347, 1242, 1083, 1016 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{34}\text{H}_{64}\text{O}_5\text{Si}_3$ ($\text{M} + \text{Na}$)⁺ 659.4062, found 659.4063.

(*R)-*tert*-Butyl 4-acetoxy-4-((3*R**,5*S**)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-((*S**)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)but-2-ynoate (133)**



To a solution of HMDS (170 μL , 0.810 mmol, 3 equiv) in dry THF (5 mL) at 0 $^{\circ}\text{C}$ was added dropwise a solution of $n\text{BuLi}$ (324 μL , 0.810 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to a solution of *tert*-butyl propiolate (102 mg, 0.810 mmol, 3 equiv) in dry THF (5 mL) at -78 $^{\circ}\text{C}$. After stirring for 10 min, aldehyde **105** (118 mg, 0.270 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 $^{\circ}\text{C}$ for 1 h. Ac_2O (153 μL , 1.61 mmol, 6 equiv) was added dropwise and the reaction was allowed to warm up to room temperature and stirred for 18 h. The reaction was then quenched with saturated aqueous NaHCO_3 and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **133** as a colourless oil (131 mg, 80%).

^1H NMR (500 MHz, CDCl_3): δ 6.73 (s, 1H, H-6), 5.89 (dddd, 1H, $J = 16.8, 10.2, 8.1, 6.4$ Hz, H-8), 5.08-4.93 (m, 2H, H-8'), 4.44 (t app, 1H, $J = 6.7$ Hz, H-3), 2.86-2.74 (m, 1H, H-1), 2.30-2.13 (m, 2H, H-9a + H-2a), 2.11 (s, 3H, OAc), 2.09-2.04 (m, 1H, H-9b), 1.87 (d, 3H, $J = 1.4$ Hz, H-15), 1.47 (s, 9H, COO^tBu), 1.31-1.24 (m, 1H, H-2b), 1.17 (s, 3H, H-14), 0.98 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.91 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.70-0.64 (m, 6H, $\text{CH}_2\text{-TES}$), 0.09 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.07 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

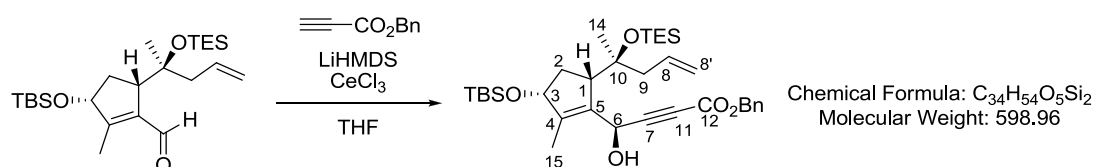
^{13}C NMR (101 MHz, CDCl_3): δ 169.2 (Ac), 152.4 (C-12), 145.6 (C-4), 135.0 (C-5), 131.4 (C-8), 117.3 (C-8'), 83.3 (C-7), 81.5 (C-11), 78.6 (C-3), 78.3 (C-10), 77.8 ($\text{Me}_3\text{C-}^t\text{Bu}$), 60.8 (C-1), 55.7 (C-6), 41.8 (C-9), 36.8 (C-2), 27.9 ($\text{Me}_3\text{C-}^t\text{Bu}$), 26.2 (C-14), 25.8 ($\text{Me}_3\text{C-}$

TBS), 20.8 (Ac) 18.1 (Me₃C-*TBS*), 13.0 (C-15), 7.3 (CH₂-*TES*), 6.9 (CH₃-*TES*), -4.4 (Me-*TBS*), -4.7 (Me-*TBS*) ppm.

IR (thin film): 2954, 2887, 2360, 1751, 1712, 1373, 1257, 1219, 1157, 1064, 1002, 840, 740 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₃H₅₈O₆Si₂ (M + Na)⁺ 629.3664, found 629.3636.

(*R*)-Benzyl 4-((3*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-((*S*)-2-(triethylsilyloxy)pent-4-en-2-yl)cyclopent-1-enyl)-4-hydroxybut-2-ynoate (134**)**



CeCl₃·7H₂O (1.28 g, 3.44 mmol, 3 equiv) was dried under vacuum at 60 °C (4 h), 80 °C (4 h), 100 °C (12 h), 140 °C (4 h), in that order. Dry THF (50 mL) was added and the white suspension was sonicated for 1 h then cooled to -78 °C. To a separate solution of HMDS (721 μL, 3.44 mmol, 3 equiv) in dry THF (5 mL) at 0 °C was added dropwise a solution of ⁿBuLi (1.38 mL, 3.44 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to the reaction mixture. Benzyl propiolate (0.44 mL, 3.44 mmol, 3 equiv) was added dropwise and after stirring at -78 °C for 10 min, aldehyde **105** (503 mg, 1.15 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous NH₄Cl, diluted with brine and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/CH₂Cl₂, 50:50 to remove benzyl propiolate, then petroleum ether/ethyl acetate, 95:5) to give **134** as a colourless oil (645 mg, 92%).

¹H NMR (400 MHz, CDCl₃): δ 7.41-7.28 (m, 5H, Ar), 5.89 (ddt app, 1H, *J* = 17.5, 10.2, 7.5 Hz, H-8), 5.27 (d, 1H, *J* = 9.2 Hz, H-6), 5.19 (s, 2H, PhCH₂), 5.09-4.95 (m, 2H, H-8'), 4.77 (d, 1H, *J* = 9.2 Hz, OH), 4.41 (dd, 1H, *J* = 7.7, 4.1 Hz, H-3), 2.94 (t app, 1H, *J* = 6.1 Hz, H-1), 2.53 (dd, 1H *J* = 14.5, 7.2 Hz, H-9a), 2.42-2.23 (m, 2H, H-2a + H-9b), 1.76 (d, 3H, *J* = 1.3 Hz, H-15), 1.33 (ddd, 1H *J* = 13.8, 5.8, 4.4 Hz, H-2b), 1.27 (s, 3H, H-14), 0.96

(t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.90 (s, 9H $\text{CH}_3\text{-TBS}$), 0.69 (q, 6H, $J = 7.9$ Hz, $\text{CH}_2\text{-TES}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.06 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

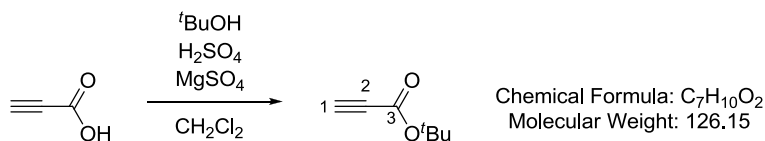
^{13}C NMR (101 MHz, CDCl_3): δ 153.3 (C-12), 142.6 (C-4), 135.1 (C-5), 134.9 (C-8), 134.9 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 117.8 (C-8'), 88.0 (C-7), 80.0 (C-11), 78.2 (C-3), 76.3 (C-10), 67.4 (PhCH_2), 59.5 (C-1), 57.3 (C-6), 42.1 (C-9), 36.4 (C-2), 26.2 (C-14), 25.8 ($\text{Me}_3\text{C-TBS}$), 18.0 ($\text{Me}_3\text{C-TBS}$), 12.5 (C-15), 7.0 ($\text{CH}_2\text{-TES}$), 6.9 ($\text{CH}_3\text{-TES}$), -4.5 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 3361, 2955, 2875, 1712, 1456, 1375, 1229, 1054, 1003, 747 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{34}\text{H}_{54}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 621.3402, found 621.3392.

$[\alpha]_{\text{D}}^{25}$ -9.7 (c 1.0, CHCl_3)

***tert*-Butyl propiolate (135)**

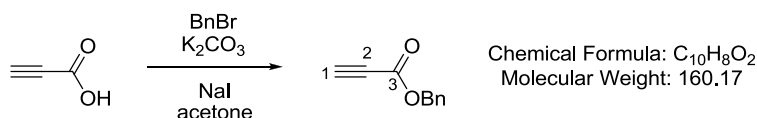


Ref: *Chem. Commun.* **2015**, 51, 13004.

To a suspension of anhydrous MgSO_4 (6.87 g, 57.1 mmol, 4 equiv) in dry CH_2Cl_2 (60 mL) was added H_2SO_4 (0.76 mL, 14.3 mmol, 1 equiv) and the resulting mixture was stirred vigorously for 15 min. Propiolic acid (0.88 mL, 14.3 mmol) was added, after which *tert*-butanol (6.78 mL, 71.3 mmol, 5 equiv) was slowly added and the reaction flask tightly stoppered. The reaction was left stirring for 24 h, after which saturated aqueous NaHCO_3 (100 mL) was added and the resulting mixture was stirred until all MgSO_4 had dissolved. The organic phase was collected, washed with brine, dried over MgSO_4 and concentrated *in vacuo* to give *tert*-butyl propiolate as a yellow oil (1.42 g, 79%).

^1H NMR (400 MHz, CDCl_3): δ 2.68 (s, 1H, H-1), 1.44 (s, 9H, COO^tBu) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 151.7 (C-3), 84.1 ($\text{Me}_3\text{C-}^t\text{Bu}$), 76.0 (C-1), 72.2 (C-2), 27.9 ($\text{Me}_3\text{C-}^t\text{Bu}$) ppm.

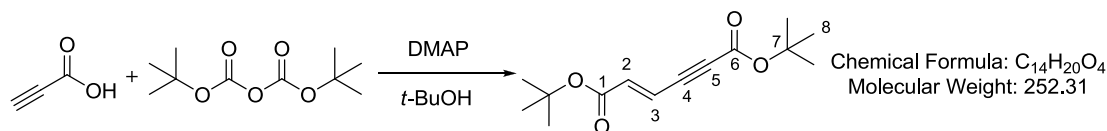
Benzyl propiolate (137)

Ref: *ChemBioChem* **2011**, *12*, 1193.

To a solution of propiolic acid (3.52 mL, 58 mmol, 1 equiv) in acetone (180 mL) was added K₂CO₃ (8.15 g, 59.0 mmol, 1.01 equiv) and NaI (870 mg, 5.80 mmol, 0.1 equiv). Benzyl bromide (6.88 mL, 58.0 mmol, 1 equiv) was added rapidly dropwise and the reaction mixture heated to reflux. The reaction mixture was left stirring at reflux for 24 h, after which it was cooled to rt and volatiles were removed *in vacuo*. The residue was partitioned between Et₂O and water, and the aqueous phase was extracted with Et₂O (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **137** as a colourless oil (8.48 g, 91%).

¹H NMR (400 MHz, CDCl₃): δ 7.51-7.34 (m, 5H, Ar), 5.25 (s, 2H, PhCH₂), 2.92 (s, 1H, H-1) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 152.5 (C-3), 134.6 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 75.0 (C-1), 74.6 (C-2), 67.9 (PhCH₂) ppm.

(E)-di-*tert*-Butyl hex-2-en-4-ynedioate (136)

To a solution of propiolic acid (1.00 g, 14.3 mmol) in *tert*-butanol (5 mL) was added di-*tert*-butyl carbonate (6.56 mL, 28.5 mmol, 2 equiv) and DMAP (0.520 g, 4.28 mmol, 0.3 equiv). The solution was left to stir for 12 h at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **136** as a yellow oil (1.37 g, 76%).

^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, 1H, $J = 12.4$ Hz, H-3), 5.54 (d, 1H, $J = 12.4$ Hz, H-5), 1.46 (s, 9H, COO^tBu), 1.41 (s, 9H, COO^tBu) ppm.

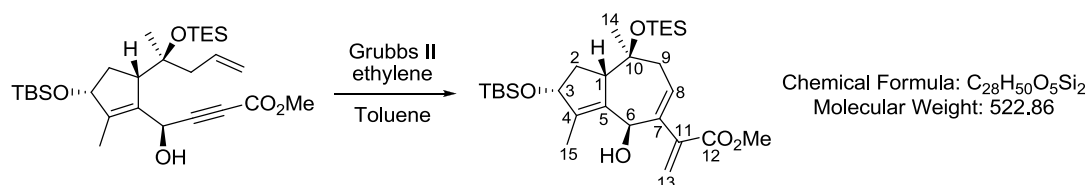
^{13}C NMR (101 MHz, CDCl_3): δ 165.4 (C-1), 150.6 (C-6), 149.7 (C-3), 107.1 (C-2), 84.9 (C-4), 81.0 (C-5), 80.7 ($\text{Me}_3\text{C}-^t\text{Bu}$), 77.2 ($\text{Me}_3\text{C}-^t\text{Bu}$), 28.2 ($\text{Me}_3\text{C}-^t\text{Bu}$), 27.6 ($\text{Me}_3\text{C}-^t\text{Bu}$) ppm.

IR (thin film): 2978, 1766, 1712, 1257, 1111 cm^{-1} .

General procedure for ring-closing ene-yne metathesis.

A solution of enyne in dry toluene [0.02 M] was degassed using the freeze-pump-thaw cycle (x3). Grubbs second-generation catalyst was added in one portion. The reaction was heated to 80 $^\circ\text{C}$ and left to stir overnight under an ethylene atmosphere. The solution was cooled to rt and concentrated *in vacuo*. The title compound was obtained after purification as indicated.

Methyl 2-((2*R*,4*S*,8*S*,8*aS*)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)acrylate (**138**)



Method 1

After following the general RCYEM procedure with enyne **128** (100 mg, 0.190 mmol), the crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 98:2) to give **138** as a colourless oil (63 mg, 63%).

Method 2

To a solution of ester **139** (25 mg, 0.042 mmol) in dry MeOH (1 mL) at -78 $^\circ\text{C}$ was added a solution of I_2 (0.53 mg, 0.0021 mmol, 0.05 equiv) in MeOH (0.2 mL) and stirred for 3.5 h. The reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine,

dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **138** as a colourless oil (16 mg, 73%).

^1H NMR (400 MHz, CDCl_3): δ 6.15 (d, 1H, $J = 1.7$ Hz, H-13a), 5.78 (d, 1H, $J = 1.7$ Hz, H-13b), 5.54 (dd, 1H, $J = 8.1, 3.0$ Hz, H-8), 4.95 (d, 1H, $J = 10.6$ Hz, H-6), 4.51 (d, 1H, $J = 10.6$ Hz, OH), 4.53-4.44 (m, 1H, H-3), 3.76 (s, 3H, COOMe), 3.03-2.95 (m, 1H, H-1), 2.52 (dd, 1H, $J = 17.1, 3.0$ Hz, H-9a), 2.34-2.16 (m, 3H, H-2 + H-9b), 1.69 (dd, 3H, $J = 2.1, 1.0$ Hz, H-15), 1.26 (s, 3H, H-14), 0.97 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$) 0.90 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.65 (q, 6H, $J = 7.9$ Hz, $\text{CH}_2\text{-TES}$), 0.09 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.07 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

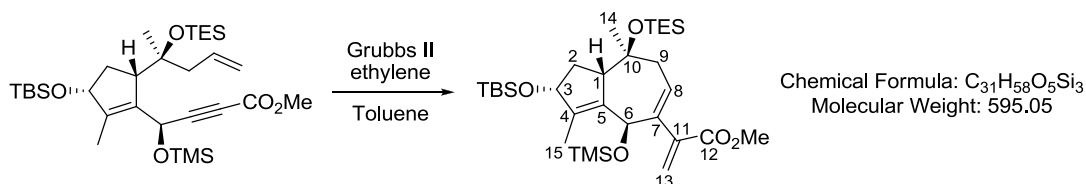
^{13}C NMR (101 MHz, CDCl_3): δ 167.4 (C-12), 142.9 (C-11), 140.5 (C-4), 137.5 (C-7), 136.1 (C-5), 130.9 (C-8), 125.1 (C-13), 79.5 (C-3), 77.8 (C-10), 68.8 (C-6), 57.8 (C-1), 52.1 (COOMe), 42.1 (C-9), 34.4 (C-2), 25.9 ($\text{Me}_3\text{C-TBS}$), 22.2 (C-14), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.1 (C-15), 7.2 ($\text{CH}_2\text{-TES}$), 6.9 ($\text{CH}_3\text{-TES}$), -4.4 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 3320, 2957, 2929, 1728, 1460, 1380, 1229, 1023 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{28}\text{H}_{50}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 545.3094, found 545.3100

$[\alpha]_D^{25}$ -44.9 (c 1.0, CHCl_3)

Methyl 2-((2R*,4S*,8S*,8aS*)-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-4-(trimethylsilyloxy)-1,2,4,7,8,8a-hexahydroazulen-5-yl)acrylate (139)



After following the general RCYEM procedure with enyne **129** (102 mg, 0.17 mmol), the crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 98:2) to give **139** as a colourless oil (102 mg, 100%).

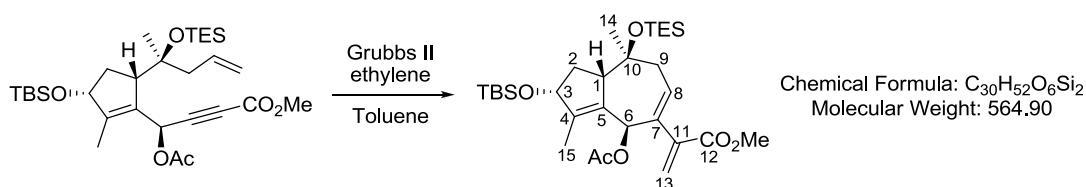
^1H NMR (400 MHz, CDCl_3): δ 6.04 (d, 1H, $J = 1.7$ Hz, H-13a), 5.84 (ddd, 1H, $J = 9.6$, 5.2, 1.3 Hz, H-8), 5.55 (d, 1H, $J = 1.7$ Hz, H-13b), 4.86 (d, 1H, $J = 1.3$ Hz, H-6), 4.42 (d, 1H, $J = 6.9$ Hz, H-3), 3.78 (s, 3H, COOMe), 3.28 (d, 1H, $J = 9.1$ Hz, H-1), 3.22 (dd, 1H, $J = 13.2$, 5.2 Hz, H-9a), 2.22-2.06 (m, 2H, H-2 + H-9b), 1.77-1.71 (m, 1H, H-2b), 1.59 (d, 3H, $J = 1.4$ Hz, H-15), 1.07 (s, 3H, H-14), 0.98 (t, 9H $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.90 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.62 (q, 6H, $J = 8.0$ Hz, $\text{CH}_2\text{-TES}$) 0.10-0.07 (m, 15H, $\text{CH}_3\text{-TBS}$ + $\text{CH}_3\text{-TMS}$) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 167.4 (C-12), 143.0 (C-11), 140.5 (C-4), 137.5 (C-7), 136.0 (C-5), 131.0 (C-8), 125.0 (C-13), 79.5 (C-3), 77.2 (C-10), 68.8 (C-6), 57.8 (C-1), 52.1 (COOMe), 42.1 (C-9), 34.3 (C-2), 25.8 ($\text{Me}_3\text{C-TBS}$), 22.2 (C-14), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.0 (C-15), 7.1 ($\text{CH}_2\text{-TES}$), 6.9 ($\text{CH}_3\text{-TES}$), 0.1 (Me-TMS), -4.4 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2956, 2930, 1727, 1435, 1379, 1360, 1245, 1093, 1020 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{31}\text{H}_{58}\text{O}_5\text{Si}_3$ ($\text{M} + \text{Na}$) $^+$ 617.3489, found 617.3489.

Methyl 2-((2*R,4*S**,8*S**,8*aS**)-4-acetoxy-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)acrylate (**140**)**



After following the general RCYEM procedure with enyne **130** (179 mg, 0.320 mmol), the reaction was filtered over celite and the filtrate concentrated *in vacuo* to give **140** as a colourless oil (179 mg, 100%).

^1H NMR (500 MHz, CDCl_3): δ 6.08 (d, 1H, $J = 1.1$ Hz, H-13a), 6.01 (d, 1H, $J = 1.1$ Hz, H-13b), 5.97 (ddd, 1H, $J = 9.6$, 5.0, 0.9 Hz, H-8), 5.62 (d, 1H, $J = 0.9$ Hz, H-6), 4.43 (dd, 1H, $J = 8.0$, 2.0 Hz, H-3), 3.74 (s, 3H, COOMe), 3.09 (d, 1H, $J = 8.4$ Hz, H-1), 3.00 (dd, 1H, $J = 13.9$, 5.1 Hz, H-9a), 2.27 (dd, 1H, $J = 13.9$, 9.6 Hz, H-9b), 2.21 – 2.13 (m, 1H, H-2a), 2.07 (s, 3H, OAc), 1.74-1.69 (m, 1H, H-2b), 1.68 (d, 3H, $J = 1.7$ Hz, H-15), 1.09 (s,

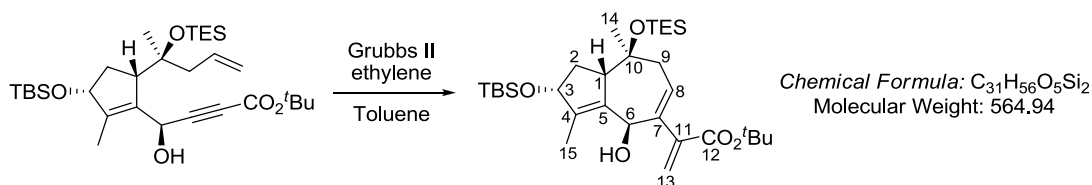
3H, H-14), 0.96 (t, 9H J = 7.9 Hz, CH₃-TES), 0.88 (s, 9H, CH₃-TBS), 0.60 (q, 6H J = 7.9 Hz, CH₂-TES), 0.07 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 170.0 (Ac), 166.8 (C-12), 142.3 (C-11), 140.8 (C-4), 137.1 (C-7), 133.2 (C-5), 132.4 (C-8), 125.8 (C-13), 78.9 (C-3), 76.3 (C-10), 70.0 (C-6), 58.2 (C-1), 52.1 (COOMe), 42.4 (C-9), 34.7 (C-2), 25.8 (Me₃C-TBS), 22.2 (C-14), 21.1 (Ac), 18.1 (Me₃C-TBS), 12.2 (C-15), 7.1 (CH₂-TES), 6.9 (CH₃-TES), -4.4 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2954, 2877, 1735, 1234, 1111, 1010, 833 cm⁻¹.

HRMS (ESI): m/z calculated for C₃₀H₅₂O₆Si₂ (M + Na)⁺ 587.3195, found 587.3168.

***tert*-Butyl 2-((2*R**,4*S**,8*S**,8*aS**)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)acrylate (**141**)**



After following the general RCYEM procedure with enyne **131** (50 mg, 0.097 mmol) at 100 °C, the crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 97:3) to give **141** as a colourless oil (11.5 mg, 23%).

¹H NMR (400 MHz, CDCl₃): δ 5.94 (d, 1H, J = 1.8 Hz, H-13a), 5.69 (d, 1H, J = 1.8 Hz, H-13b), 5.59 (dd, 1H, J = 7.6, 3.8 Hz, H-8), 4.92 (d, 1H, J = 9.6 Hz, H-6), 4.46 (t app, 1H, J = 6.7 Hz, H-3), 4.31 (d, 1H, J = 9.6 Hz, OH), 3.02 (t app, 1H, J = 7.2 Hz, H-1), 2.48 (dd, 1H, J = 16.7, 3.8 Hz, H-9a), 2.37-2.20 (m, 2H, H-9b + H-2a), 1.68 (dd, 3H, J = 2.0, 0.9 Hz, H-15), 1.51 (s, 9H, COO^tBu), 1.46-1.39 (m, 1H, H-2b), 1.23 (s, 3H, H-14), 0.97 (t, 9H, J = 7.9 Hz, CH₃-TES), 0.89 (s, 9H, CH₃-TBS), 0.64 (q, 6H J = 8.0 Hz, CH₂-TES), 0.07 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS) ppm.

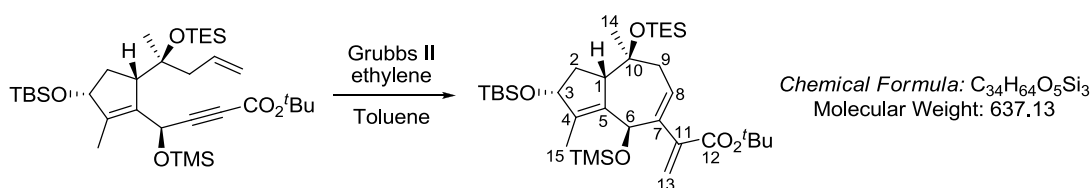
¹³C NMR (101 MHz, CDCl₃): δ 166.5 (C-12), 144.7 (C-11), 141.4 (C-4), 139.3 (C-7), 137.2 (C-5), 128.2 (C-8), 124.2 (C-13), 81.0 (C-3), 78.9 (C-10), 77.9 (Me₃C-^tBu), 67.8 (C-6), 55.0 (C-1), 38.6 (C-9), 37.6 (C-2), 28.0 (Me₃C-^tBu), 26.8 (C-14), 25.9 (Me₃C-TBS),

18.1 (Me₃C-*TBS*), 11.4 (C-15), 7.0 (CH₂-*TES*), 6.6 (CH₃-*TES*), -4.4 (Me-*TBS*), -4.8 (Me-*TBS*) ppm.

IR (thin film): 3726, 3626, 2924, 1712, 1458, 1429, 1149, 1002, 840, 671 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₁H₅₆O₅Si₂ (M + Na)⁺ 587.3581, found 587.3593.

***tert*-Butyl 2-((2*R**,4*S**,8*S**,8*aS**)-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-4-(trimethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)acrylate (142)**



After following the general RCYEM procedure with enyne **132** (62 mg, 0.097 mmol) the crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **142** as a colourless oil (47 mg, 76%).

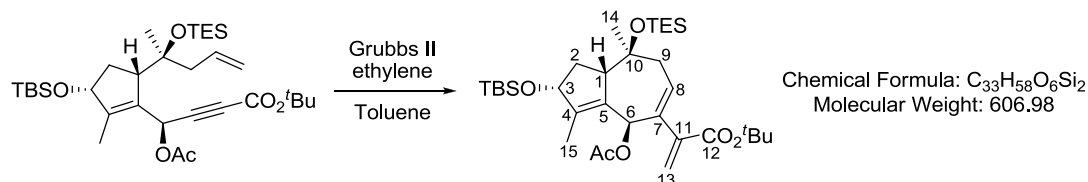
¹H NMR (500 MHz, CDCl₃): δ 5.84 (d, 1H, *J* = 1.6 Hz, H-13a), 5.80 (ddd, 1H, *J* = 9.8, 5.1, 1.1 Hz, H-8), 5.47 (d, 1H, *J* = 1.5 Hz, H-13b), 4.86 (d, 1H, *J* = 1.1 Hz, H-6), 4.40 (d, 1H, *J* = 6.8 Hz, H-3), 3.25 (d, 1H, *J* = 8.9 Hz, H-1), 3.17 (dd, 1H, *J* = 13.3, 5.1 Hz, H-9a), 2.18-2.06 (m, 2H, H-9b + H-2a), 1.74-1.68 (m, 1H, H-2b), 1.60 (d, 3H, *J* = 1.1 Hz, H-15), 1.48 (s, 9H, COO^tBu), 1.06 (s, 3H, H-14), 0.96 (t, 9H, *J* = 7.9 Hz, CH₃-*TES*), 0.88 (s, 9H, CH₃-*TBS*), 0.59 (q, 6H, *J* = 7.9 Hz, CH₂-*TES*), 0.08-0.04 (m, 15H, CH₃-*TBS* + CH₃-*TMS*) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 166.3 (C-12), 144.8 (C-11), 140.3 (C-4), 137.7 (C-7), 135.8 (C-5), 130.4 (C-8), 122.1 (C-13), 80.8 (C-3), 79.4 (C-10), 76.8 (Me₃C-^tBu), 68.8 (C-6), 57.5 (C-1), 42.1 (C-9), 34.3 (C-2), 28.0 (Me₃C-^tBu), 25.6 (Me₃C-*TBS*), 22.3 (C-14), 18.0 (Me₃C-*TBS*), 12.1 (C-15), 7.1 (CH₂-*TES*), 6.8 (CH₃-*TES*), 0.0 (Me-*TMS*), -4.4 (Me-*TBS*), -4.8 (Me-*TBS*) ppm.

IR (thin film): 2954, 2877, 2360, 1712, 1458, 1365, 1249, 1141, 1111, 1018, 887, 840, 740 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{34}\text{H}_{64}\text{O}_5\text{Si}_3$ ($\text{M} + \text{Na}$)⁺ 659.3954, found 659.3921.

***tert*-Butyl 2-((2*R**,4*S**,8*S**,8*aS**)-4-acetoxy-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)acrylate (**143**)**



After following the general RCYEM procedure with enyne **133** (131 mg, 0.220 mmol) the crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **143** as a colourless oil (122 mg, 93%).

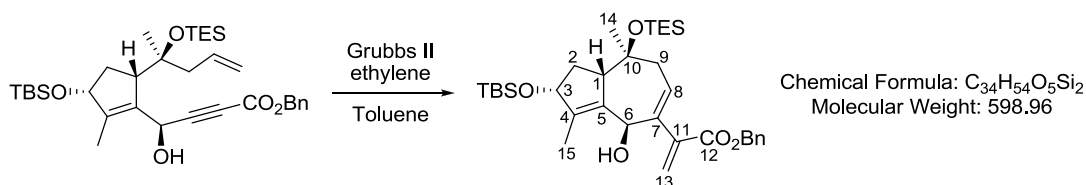
¹H NMR (400 MHz, CDCl_3): δ 5.98 (s, 1H, H-6), 5.94 (d, 1H, $J = 1.5$ Hz, H-13a), 5.97-5.91 (m, 1H, H-8), 5.53 (d, 1H, $J = 1.4$ Hz, H-13b), 4.43 (d, 1H, $J = 6.1$ Hz, H-3), 3.04 (t app, 1H, $J = 8.6$ Hz, H-1), 2.99 (d, 1H, $J = 5.1$ Hz, H-9a), 2.32-2.11 (m, 2H, H-9b + H-2a), 2.06 (s, 3H, OAc), 1.68 (d, 3H, $J = 1.5$ Hz, H-15), 1.72-1.64 (m, 1H, H-2b), 1.48 (s, 9H, COO^tBu), 1.09 (s, 3H, H-14), 0.96 (t, 9H, $J = 7.8$ Hz, $\text{CH}_3\text{-TES}$), 0.87 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.60 (q, 6H, $J = 7.9$ Hz, $\text{CH}_2\text{-TES}$), 0.06 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.05 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

¹³C NMR (101 MHz, CDCl_3): δ 170.0 (Ac), 165.9 (C-12), 144.0 (C-11), 140.6 (C-4), 137.1 (C-7), 132.5 (C-5), 132.5 (C-8), 124.3 (C-13), 81.4 (C-3), 78.9 (C-10), 76.4 ($\text{Me}_3\text{C-}^t\text{Bu}$), 70.3 (C-6), 58.2 (C-1), 42.4 (C-9), 34.6 (C-2), 28.0 ($\text{Me}_3\text{C-}^t\text{Bu}$), 25.8 ($\text{Me}_3\text{C-TBS}$), 22.3 (C-14), 21.2 (Ac), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.3 (C-15), 7.2 ($\text{CH}_2\text{-TES}$), 6.9 ($\text{CH}_3\text{-TES}$), -4.5 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2954, 2877, 2160, 1735, 1720, 1458, 1365, 1234, 1149, 1111, 1064, 1010, 956, 840 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{33}\text{H}_{58}\text{O}_6\text{Si}_2$ ($\text{M} + \text{Na}$)⁺ 629.3664, found 629.3659.

Benzyl 2-((2*R*,4*S*,8*S*,8*aS*)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)acrylate (144**)**



After following the general RCYEM procedure with enyne **134** (645 mg, 1.08 mmol) the crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **144** as a colourless oil (300 mg, 47%).

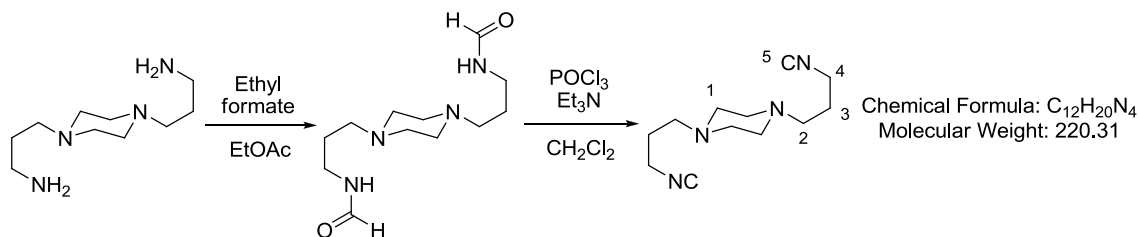
¹H NMR (400 MHz, CDCl₃): δ 7.43-7.26 (m, 5H, Ar), 6.16 (d, 1H, *J* = 1.6 Hz, H-13a), 5.82 (d, 1H, *J* = 1.6 Hz, H-13b), 5.59 (dd, 1H, *J* = 8.0, 3.3 Hz, H-8), 5.22 (s, 2H, PhCH₂), 4.97 (d, 1H, *J* = 10.1 Hz, H-6), 4.46 (t app, 1H, *J* = 6.8 Hz, H-3), 4.40 (d, 1H, *J* = 10.1 Hz, OH), 3.00 (t app, 1H, *J* = 7.2 Hz, H-1), 2.50 (dd, 1H, *J* = 16.9, 3.3 Hz, H-9a), 2.33-2.21 (m, 2H, H-2a + H-9b), 1.63 (dd, 3H, *J* = 1.9, 0.9 Hz, H-15), 1.29-1.18 (m, 4H, H-14 + H-2b), 0.96 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.90 (s, 9H, CH₃-TBS), 0.64 (q, *J* = 7.7 Hz, 6H, CH₂-TES), 0.08 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS).

¹³C NMR (101 MHz, CDCl₃): δ 166.8 (C-12), 142.9 (C-11), 140.8 (C-4), 139.4 (C-7), 137.3 (C-5), 135.9 (C-Ar), 128.6 (C-8), 128.5 (C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 126.3 (C-13), 79.0 (C-3), 77.8 (C-10), 67.7 (C-6), 66.6 (PhCH₂), 54.7 (C-1), 38.30 (C-9), 37.8 (C-2), 27.1 (C-14), 25.9 (Me₃C-TBS), 18.2 (Me₃C-TBS), 11.3 (C-15), 6.9 (CH₂-TES), 6.6 (CH₃-TES), -4.4 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 3452, 2953, 2875, 1716, 1456, 1249, 1136, 1002, 835 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₄H₅₄O₅Si₂ (M + Na)⁺ 621.3402, found 621.3380.

[α]_D²⁵ -28.1 (*c* 1.0, CHCl₃)

1,4-bis(3-Isocyanopropyl)piperazine (163)

Ref: *ChemSusChem*, **2015**, 8, 4139.

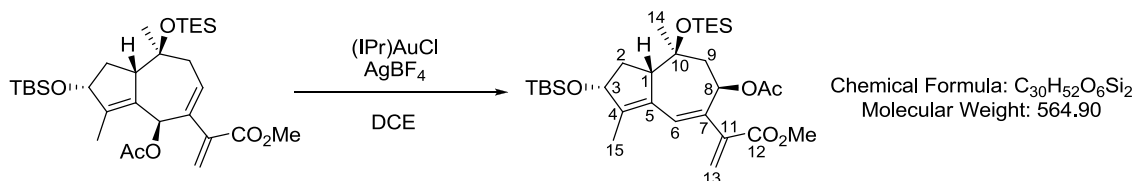
To a solution of ethyl formate (8.25 mL, 100 mmol, 5 equiv) in ethyl acetate (12.5 mL) at room temperature was added dropwise 1,4-bis(3-aminopropyl)piperazine **165** (4.12 mL, 20.0 mmol, 1 equiv). The reaction mixture was stirred for 2 h at room temperature, after which ethyl acetate (10 mL) was added and the white precipitate filtered off. The residue was washed with ethyl acetate and dried *in vacuo*. The residue was then redissolved in CH₂Cl₂ (100 mL), and Et₃N (33.4 mL, 240 mmol, 12 equiv) was added dropwise at room temperature. The solution was then cooled down to 0 °C and phosphoryl chloride (5.59 mL, 60.0 mmol, 3 equiv) added dropwise. The reaction was stirred at 0 °C for 15 min, after which the temperature was raised to room temperature and stirring maintained for a further 1 h. Under ice-cooling, saturated aqueous K₂CO₃ (150 mL) was slowly added and the resulting mixture stirred for 30 min. The aqueous phase was then extracted with CH₂Cl₂ (x3) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was transferred to a pad of silica and washed with a solution of CH₂Cl₂ and Et₃N (100:2). The solvent was removed *in vacuo* and the residue recrystallised from cyclohexane to give **163** as a white crystalline solid (775 mg, 18% over two steps).

m.p. 74-76 °C (ref: 79-81 °C)

¹H NMR (400 MHz, CDCl₃): δ 3.62-3.34 (m, 4H, H-4), 2.72-2.15 (m, 12H, H-1 + H-2), 1.94-1.76 (m, 4H, H-3) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 156.0 (C-5), 54.4 (C-1), 53.1 (C-2), 39.5 (C-4), 26.4 (C-3) ppm.

Methyl 2-((2*R,6*R**,8*S**,8*aS**)-6-acetoxy-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-1,2,6,7,8,8*a*-hexahydroazulen-5-yl)acrylate (**166**)**



To a solution of (IPr)AuCl (0.82 mg, 0.0013 mmol, 0.03 equiv) in dry 1,2-dichloroethane (0.5 mL) was added AgBF₄ (0.17 mg, 0.00089 mmol, 0.02 equiv) in 1,2-dichloroethane (0.5 mL). The solution was left to stir for 1 minute at room temperature, after which a solution of **140** (25 mg, 0.044 mmol) in 1,2-dichloroethane (0.5 mL) was added and the sealed vial placed in a scientific microwave reactor. The reaction mixture was stirred at 80 °C for 30 min and allowed to cool to room temperature. The solution was diluted with pentane and filtered over celite, the filtrate concentrated *in vacuo* and the residue purified by flash column chromatography (petroleum ether/ethyl acetate, 98:2) to give **166** as a colourless oil (6.9 mg, 28% dr 3:1).

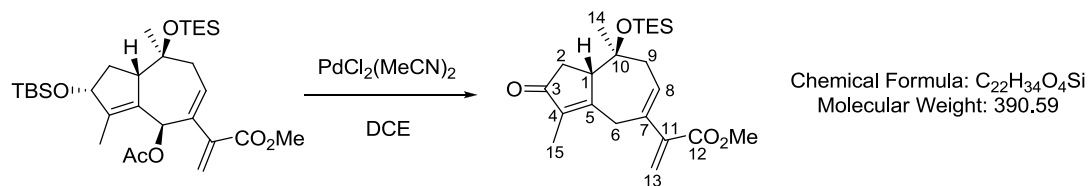
¹H NMR (400 MHz, CDCl₃): δ 6.37 (s, 1H, H-6), 6.06 (d, 1H, *J* = 1.5 Hz, H-13a), 5.68 (dd, 1H, *J* = 10.7, 3.8 Hz, H-8), 5.62 (d, 1H, *J* = 1.5 Hz, H-13b), 4.50 (t app, 1H, *J* = 6.6 Hz, H-3), 3.72 (s, 3H, COOMe), 2.84 (t app, 1H, *J* = 7.6 Hz, H-1), 2.37-2.21 (m, 2H, H-2a + H-9a), 2.06-1.93 (m, 4H, H-2b + Ac), 1.74 (s, 3H, H-15), 1.64-1.57 (m, 1H, H-9b), 1.21 (s, 3H, H-14), 0.94 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.91 (s, 9H, CH₃-TBS), 0.58 (q, 6H, *J* = 7.9 Hz, CH₂-TES), 0.10 (s, 3H, CH₃-TBS), 0.09 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 169.7 (Ac), 167.1 (C-12), 146.9 (C-5), 144.0 (C-11), 137.0 (C-7), 132.2 (C-4), 125.8 (C-13), 125.1 (C-6), 78.0 (C-3), 74.4 (C-10), 70.8 (C-8), 57.3 (C-1), 52.0 (COOMe), 48.3 (C-9), 35.9 (C-2), 25.9 (Me₃C-TBS), 21.5 (C-14), 21.0 (Ac), 18.2 (Me₃C-TBS), 12.2 (C-15), 7.1 (CH₂-TES), 6.8 (CH₃-TES), -4.4 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 2957, 2880, 1736, 1458, 1230, 1111, 1012 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₀H₅₂O₆Si₂ (M + Na)⁺ 587.3195, found 587.3192.

Methyl 2-((8*S,8*aS**)-3,8-dimethyl-2-oxo-8-(triethylsilyloxy)-1,2,4,7,8,8a-hexahydroazulen-5-yl)acrylate (**172**)**



To a solution of acetate **140** (25 mg, 0.044 mmol) in dry 1,2-dichloroethane (2 mL) was added (MeCN)₂PdCl₂ (0.22 mg, 0.00089 mmol, 0.02 equiv) in 1,2-dichloromethane (2 mL). The solution was stirred at room temperature for 2.5 h, after which the solution was concentrated *in vacuo* and the residue purified by flash column chromatography (petroleum ether/ethyl acetate, 90:10) to give **172** as a yellow oil (11.0 mg, 64%).

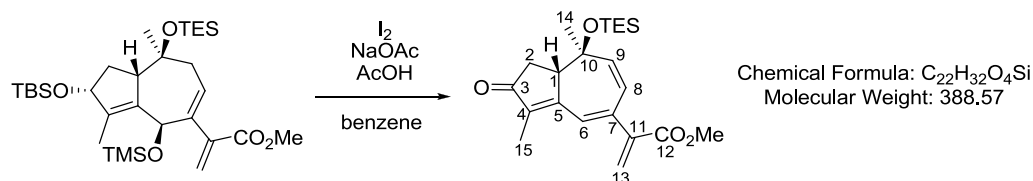
¹H NMR (400 MHz, CDCl₃): δ 6.03 (d, 1H, *J* = 1.5 Hz, H-13a), 5.87 (dd, 1H, *J* = 7.9, 6.0 Hz, H-8), 5.58 (d, 1H, *J* = 1.5 Hz, H-13b), 3.78 (s, 3H, COOMe), 3.35 (d, 1H, *J* = 14.1 Hz, H-6a), 3.26 (d, 1H, *J* = 14.1 Hz, H-6b), 3.06 (br s app, 1H, H-1), 2.70 (dd, 1H, *J* = 13.3, 5.1 Hz, H-2a), 2.45-2.31 (m, 3H, H-2a + H-9), 1.64 (s, 3H, H-15), 1.25 (s, 3H, H-14), 1.03-0.77 (m, 9H, CH₂-TES), 0.69-0.49 (m, 9H, CH₂-TES) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 209.5 (C-3), 166.9 (C-12), 166.8 (C-5), 143.3 (C-11), 137.1 (C-7), 135.9 (C-4), 128.8 (C-13), 124.77 (C-8), 76.5 (C-10), 57.4 (C-1), 52.2 (COOMe), 42.8 (C-9), 38.3 (C-2), 33.2 (C-6), 21.5 (C-14), 8.1 (C-15), 7.1 (CH₃-TES), 6.8 (CH₃-TES) ppm.

IR (thin film): 2952, 2878, 1713, 1642, 1137, 1107, 1010 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₂H₃₄O₄Si (M + Na)⁺ 413.2119, found 413.2115.

Methyl 2-((8*S,8*aS**)-3,8-dimethyl-2-oxo-8-(triethylsilyloxy)-1,2,8,8a-tetrahydroazulen-5-yl)acrylate (**194**)**



To a solution of silyl ether **139** (100 mg, 0.168 mmol) in dry benzene (10 mL) was added glacial acetic acid (1 mL), iodine (85.3 mg, 0.336 mmol, 2 equiv) and sodium acetate (27.6 mg, 0.336 mmol, 2 equiv) in that order. The reaction mixture was heated to reflux and stirred in the absence of light for 30 min. The reaction mixture was cooled to rt after which the solution was concentrated *in vacuo* and the residue purified by flash column chromatography (petroleum ether/ethyl acetate, 90:10) to give **194** as a yellow oil (9.2 mg, 14%).

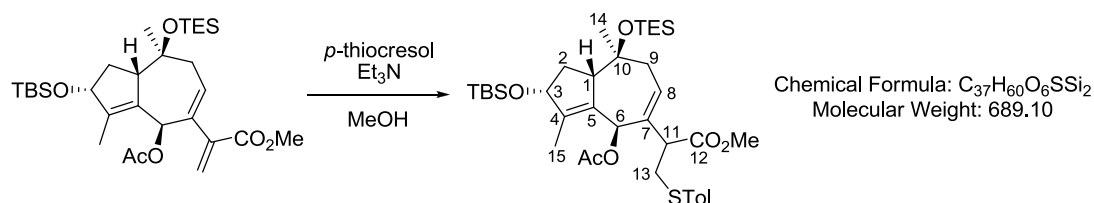
¹H NMR (400 MHz, CDCl₃): δ 6.68 (s, 1H, H-6), 6.30 (dd, 1H, *J* = 12.4, 0.5 Hz, H-8), 6.29 (d, 1H, *J* = 1.0 Hz, H-13a), 5.85-5.78 (m, 2H, H-9 + H-13b), 3.81 (s, 3H, COOMe), 3.31 (br s app, 1H, H-1), 2.52-2.46 (m, 2H, H-2), 1.85 (d, *J* = 2.1 Hz, 3H, H-15), 1.01 (s, 3H, H-14), 0.98 (t, 9H, *J* = 7.9 Hz, CH₂-TES), 0.65 (q, 5H, *J* = 7.8 Hz, CH₂-TES) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 208.2 (C-3), 166.5 (C-12), 161.1 (C-5), 146.1 (C-11), 144.0 (C-7), 140.0 (C-4), 139.2 (C-8), 127.2 (C-6), 125.2 (C-13), 122.6 (C-9), 75.7 (C-10), 52.4 (COOMe), 48.7 (C-1), 37.3 (C-2), 20.0 (C-14), 8.5 (C-15), 7.1 (CH₃-TES), 6.7 (CH₃-TES) ppm.

IR (thin film): 2953, 2875, 1726, 1695, 1381, 1139, 1006, 727 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₂H₃₂O₄Si (M + Na)⁺ 411.1962, found 411.1946.

Methyl 2-((2*R,4*R**,8*S**,8*aS**)-4-acetoxy-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)-3-(*p*-tolylthio)propanoate (**196**)**



To a solution of acetate **140** (100 mg, 0.177 mmol) in dry methanol (10 mL) was added *p*-thiocresol (44.0 mg, 0.354 mmol, 2 equiv), and triethylamine (24 μ L, 0.177 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and washed with 1 M aqueous HCl (x2), brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/diethyl ether, 95:5) to give **196** as a colourless oil (59 mg, 48%, dr 3:1). Major diastereomer peaks reported.

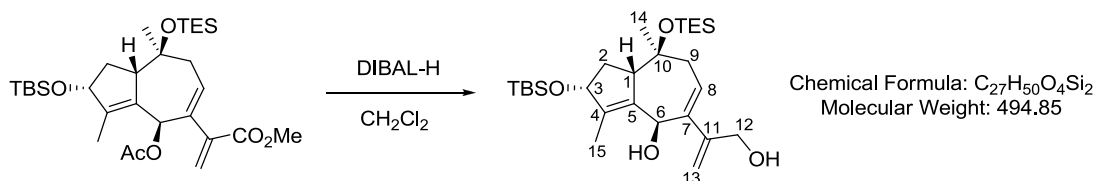
¹H NMR (500 MHz, CDCl₃): δ 7.31-7.23 (m, 2H, Ar), 7.15-7.05 (m, 2H, Ar), 5.81-5.75 (m, 2H, H-8 + H-6), 4.44-4.36 (m, 1H, H-3), 3.61 (s, 3H, COOMe), 3.37-3.21 (m, 2H, H-13a + H-11), 3.13-3.01 (m, 2H, H-1 + H-13b), 2.90 (dd, 1H, J = 13.8, 4.9 Hz, H-9a), 2.32 (s, 3H, ArMe), 2.24-2.10 (m, 2H, H-9a + H-2a), 2.03 (s, 1H, Ac), 1.71-1.64 (m, 4H, H-2b + H-15), 1.02 (s, 3H, H-14), 0.96 (t, 4H, J = 7.9 Hz, CH₃-TES), 0.87 (s, 9H, CH₃-TBS), 0.59 (q, 6H, J = 7.9 Hz, CH₂-TES), 0.06 (s, 3H, CH₃-TBS), 0.05 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 172.4 (C-12), 170.0 (Ac), 140.4 (C-4), 136.5 (C-7), 136.4 (Ar), 132.3 (C-5), 131.7 (C-8), 131.6 (Ar), 130.5 (Ar), 129.8 (Ar), 79.0 (C-3), 76.2 (C-10), 71.5 (C-6), 58.4 (C-1), 52.5 (COOMe), 51.9 (C-11), 41.9 (C-9), 35.3 (C-13), 34.5 (C-2), 25.8 (Me₃C-TBS), 22.0 (C-14), 21.0 (Ac), 21.0 (ArMe), 18.0 (Me₃C-TBS), 12.3 (C-15), 7.1 (CH₂-TES), 6.9 (CH₃-TES), -4.5 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2950, 2876, 1743, 1697, 1381, 1141, 1008 cm⁻¹.

HRMS (ESI): m/z calculated for C₃₇H₆₀O₆SSi₂ (M + Na)⁺ 711.3547, found 711.3523.

(2*R,4*R**,8*S**,8*aS**)-2-(*tert*-Butyldimethylsilyloxy)-5-(3-hydroxyprop-1-en-2-yl)-3,8-dimethyl-8-(triethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-4-ol (**197**)**



To solution to acetate **140** (90 mg, 0.159 mmol) in CH₂Cl₂ (10 mL) at -78 °C was added dropwise a solution of DIBAL-H (700 µL, 0.700 mmol, 4.4 equiv). The reaction mixture was stirred at -78 for 2 h. The reaction was quenched with the addition of MeOH (2 mL) followed by a saturated aqueous solution of Rochelle's salt. The aqueous phase was extracted with CH₂Cl₂ (x3) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/diethyl ether, 90:10) to give **197** as a colourless oil (39.1 mg, 50%).

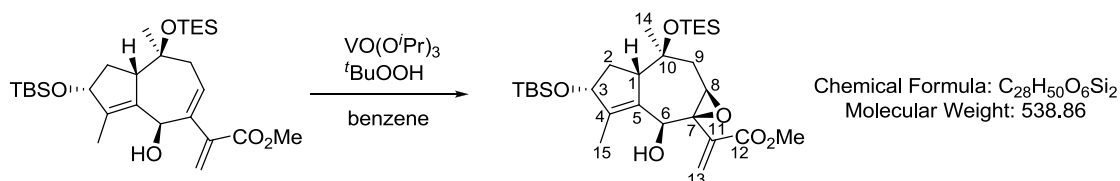
¹H NMR (500 MHz, CDCl₃): δ 5.63 (dd, 1H, *J* = 8.4, 2.3 Hz, H-8), 5.21-5.11 (m, 2H, H-13a + H-6), 5.04 (d, 1H, *J* = 1.0 Hz, H-13b), 4.96 (d, 1H, *J* = 11.1 Hz, OH), 4.48 (br t app, 1H, *J* = 7.0 Hz, H-3), 4.41 (dd, 1H, *J* = 13.4, 4.7 Hz, H-12a), 4.22 (dd, 1H, *J* = 13.4, 7.4 Hz, H-12b), 3.02-2.89 (m, 1H, H-1), 2.83 (dd, 1H, *J* = 7.4, 5.6 Hz, OH), 2.48 (dd, 1H, *J* = 17.3, 2.1 Hz, H-9a), 2.30 (dt app, 1H *J* = 12.2, 6.7 Hz, H-2a), 2.22 (ddd, 1H, *J* = 17.3, 8.4, 1.8 Hz, H-9b), 1.61 (dd, 3H, *J* = 2.1, 1.1 Hz, H-15), 1.29 (s, 3H, H-14), 1.16 (ddd, 1H, *J* = 12.2, 10.0, 7.8 Hz, H-2b), 0.95 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.90 (s, 9H, CH₃-TBS), 0.65 (q, 6H, *J* = 7.8 Hz, CH₂-TES), 0.09 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 150.1 (C-4), 141.3 (C-7), 138.9 (C-5), 137.7 (C-8), 125.8 (C-11), 111.8 (C-13), 79.4 (C-3), 77.7 (C-10), 67.4 (C-12), 65.5 (C-6), 54.4 (C-1), 38.3 (C-9), 37.8 (C-2), 27.8 (C-14), 25.9 (Me₃C-TBS), 18.2 (Me₃C-TBS), 11.3 (C-15), 6.9 (CH₂-TES), 6.4 (CH₃-TES), -4.4 (Me-TBS), -4.7 (Me-TBS) ppm.

IR (thin film): 3381, 2948, 2870, 1427, 1372, 1105, 1005 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₇H₅₀O₄Si₂ (M + Na)⁺ 517.3140, found 517.3114.

Methyl 2-((1a*S*,2*S*,4*R*,5a*S*,6*S*,7a*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-3,6-dimethyl-6-(triethylsilyloxy)-1a,2,4,5,5a,6,7,7a-octahydroazuleno[5,6-*b*]oxiren-1a-yl)acrylate (169**)**



To a solution of **138** (29.0 mg, 0.0550 mmol) in dry benzene (0.5 mL) was added VO(O^{*i*}Pr)₃ (0.315 μL, 0.00139 mmol, 0.025 equiv) in benzene (0.5 mL) and ^{*t*}BuOOH (15.0 μL, 0.0833 mmol, 1.5 equiv, 5.5M in decane) in benzene (0.5 mL) and the reaction mixture was stirred for 2 h. The reaction mixture was filtered through celite with 80:20 petroleum ether/ethyl acetate and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **169** as a colourless oil (24.8 mg, 83%).

¹H NMR (400 MHz, CDCl₃): δ 6.34 (s, 1H, H-13a), 5.72 (s, 1H, H-13b), 4.81 (s, 1H, H-6), 4.40 (d, 1H, *J* = 7.7 Hz, H-3), 3.84 (s, 3H, CH₃ ester), 3.10 (dd, 1H, *J* = 7.1, 3.9 Hz, H-8), 3.09 (d, 1H, *J* = 7.7 Hz, H-1), 2.57 (br s, 1H, OH), 2.38 (dd, 1H, *J* = 13.2, 7.7 Hz, H-9a), 2.22 (dd, 1H, *J* = 13.2, 7.7 Hz, H-9b), 2.11 (ddd, 1H, *J* = 15.0, 9.1, 7.1 Hz, H-2a), 1.76-1.70 (m, 1H, H-2b), 1.53 (d, 3H *J* = 1.8 Hz, H-15), 1.26 (s, 3H, H-14), 0.95 (t, 9H, *J* = 7.7 Hz, CH₃-TES), 0.88 (s, 9H, CH₃-TBS), 0.59 (q, 6H, *J* = 7.7 Hz, CH₂-TES), 0.08 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS) ppm.

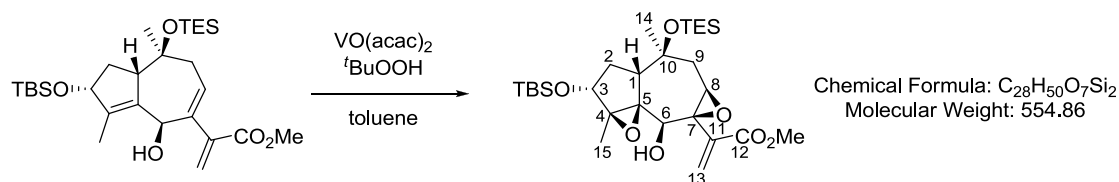
¹³C NMR (101 MHz, CDCl₃): δ 165.4 (C-12), 141.0 (C-4), 138.8 (C-11), 135.3 (C-5), 128.9 (C-13), 79.4 (C-3), 76.1 (C-10), 65.8 (C-6), 62.3 (C-7), 58.7 (C-8), 56.6 (C-1), 52.2 (COOMe), 43.1 (C-9), 34.1 (C-2), 25.8 (Me₃C-TBS), 22.9 (C-14), 18.0 (Me₃C-TBS), 12.6 (C-15), 7.1 (CH₂-TES), 6.8 (CH₃-TES), -4.5 (Me-TBS), -5.0 (Me-TBS) ppm.

IR (thin film): 3357, 2925, 2855, 1727, 1444, 1110, 1003, 756 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₈H₅₀O₆Si₂ (M + Na)⁺ 561.3038, found 561.3013.

[α]_D²⁵ +64.1 (*c* 1.0, CHCl₃)

Methyl 2-((1*S,2*R**,3*S**,5*R**,7*S**,8*S**,10*R**,11*S**)-10-(*tert*-butyldimethylsilyloxy)-2-hydroxy-7,11-methyl-7-(triethylsilyloxy)-4,12-dioxatetracyclo[6.4.0.0.^{1,11}.0^{3,5}]dodecan-3-yl)acrylate (**202**)**



To a solution of **138** (63.0 mg, 0.120 mmol) in dry toluene (2 mL) was added VO(acac)₂ (0.795 mg, 0.00300 mmol, 0.025 equiv) in toluene (0.5 mL) and *t*BuOOH (18.1 μ L, 0.0833 mmol, 1.5 equiv, 5.5M in decane) in toluene (0.5 mL) and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through celite with 80:20 petroleum ether/ethyl acetate and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **202** as a colourless oil (13.0 mg, 20%).

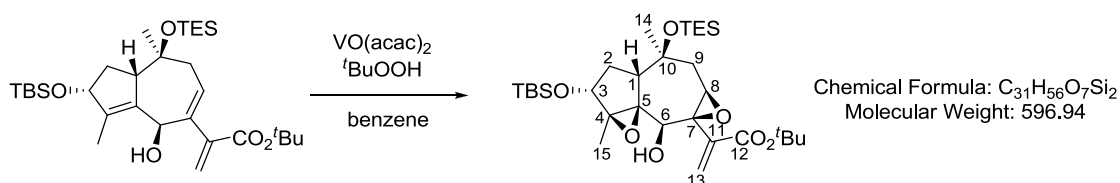
¹H NMR (500 MHz, CDCl₃): δ 6.45 (s, 1H, H-13a), 5.84 (s, 1H, H-13b), 4.09 (d, 1H, *J* = 6.6 Hz, H-3), 3.96 (s, 1H, H-6), 3.82 (s, 3H, COOMe), 3.29 (br t app, 1H, *J* = 7.2 Hz, H-8), 2.78 (d, 1H, *J* = 9.2 Hz, H-1), 2.66 (s, 1H, OH), 2.40 (dd, 1H, *J* = 13.2, 6.9 Hz, H-9a), 2.34 (dd, 1H, *J* = 13.2, 8.0 Hz, H-9b), 1.86 (ddd, 1H, *J* = 15.0, 9.4, 6.7 Hz, H-2a), 1.64 (dd, 1H, *J* = 15.0, 0.9 Hz, H-2b), 1.38 (s, 3H, H-15), 1.22 (s, 3H, H-14), 0.94 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.89 (s, 9H, CH₃-TBS), 0.58 (q, 6H, *J* = 7.9 Hz, CH₂-TES), 0.09 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 165.1 (C-12), 138.1 (C-11), 129.4 (C-13), 75.5 (C-3), 74.4 (C-6), 71.3 (C-4), 70.8 (C-7), 70.6 (C-10), 59.5 (C-5), 58.3 (C-8), 53.6 (C-1), 52.5 (COOMe), 42.2 (C-9), 33.0 (C-2), 26.0 (C-14), 25.8 (Me₃C-TBS), 18.0 (Me₃C-TBS), 14.0 (C-15), 7.1 (CH₂-TES), 6.7 (CH₃-TES), -4.5 (Me-TBS), -5.2 (Me-TBS) ppm.

IR (thin film): 3350, 2924, 2854, 1728, 1442, 1110, 1002 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₈H₅₀O₇Si₂ (M + Na)⁺ 577.2987, found 577.2961.

***tert*-Butyl 2-((1*S**,2*R**,3*S**,5*R**,7*S**,8*S**,10*R**,11*S**)-10-(*tert*-butyldimethylsilyloxy)-2-hydroxy-7,11-methyl-7-(triethylsilyloxy)-4,12-dioxatetracyclo[6.4.0.0^{1,11}.0^{3,5}]dodecan-3-yl)acrylate (**203**)**



To a solution of **142** (4.70 mg, 0.00900 mmol) in dry benzene (1 mL) was added VO(acac)₂ (0.06 mg, 0.00022 mmol, 0.01 equiv) in benzene (0.5 mL) and *t*BuOOH (1.46 μ L, 0.0130 mmol, 1.5 equiv, 5.5M in decane) in benzene (0.5 mL) and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through celite with 80:20 petroleum ether/ethyl acetate and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **203** as a colourless oil (3.6 mg, 73%).

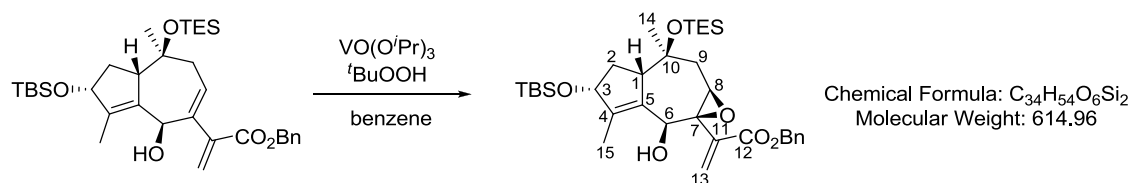
¹H NMR (400 MHz, CDCl₃): δ 6.36 (d, 1H, *J* = 0.7 Hz, H-13a), 5.73 (d, 1H, *J* = 0.7 Hz, H-13b), 4.10 (d, 1H, *J* = 6.5 Hz, H-3), 3.95 (s, 1H, H-6), 3.27 (br t app, 1H, *J* = 7.2 Hz, H-8), 2.77 (d, 1H, *J* = 9.1 Hz, H-1), 2.63 (s, 1H, OH), 2.38 (dd, 1H, *J* = 13.2, 7.0 Hz, H-9a), 2.32 (dd, 1H, *J* = 13.2, 8.0 Hz, H-9b), 1.86 (ddd, 1H, *J* = 15.0, 9.4, 6.7 Hz, H-2a), 1.63 (dd, 1H, *J* = 15.0, 0.9 Hz, H-2b), 1.52 (s, 9H, COO*t*Bu), 1.37 (s, 3H, H-15), 1.22 (s, 3H, H-14), 0.94 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.89 (s, 9H, CH₃-TBS), 0.58 (q, 6H, *J* = 7.9 Hz, CH₂-TES), 0.09 (s, 3H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 163.6 (C-12), 139.6 (C-11), 128.3 (C-13), 82.2 (Me₃C-*t*Bu), 75.5 (C-3), 74.5 (C-6), 71.3 (C-4), 70.8 (C-7), 70.7 (C-10), 59.5 (C-5), 58.2 (C-8), 53.6 (C-1), 42.2 (C-9), 33.0 (C-2), 28.1 (Me₃C-*t*Bu), 26.0 (C-14), 25.8 (Me₃C-TBS), 18.0 (Me₃C-TBS), 14.0 (C-15), 7.1 (CH₂-TES), 6.7 (CH₃-TES), -4.5 (Me-TBS), -5.1 (Me-TBS) ppm.

IR (thin film): 2924, 2877, 1720, 1458, 1080, 1010, 671 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₁H₅₆O₇Si₂ (M + Na)⁺ 619.3462, found 619.3424.

Benzyl 2-((1a*S*,2*S*,4*R*,5a*S*,6*S*,7a*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-3,6-dimethyl-6-(triethylsilyloxy)-1a,2,4,5,5a,6,7,7a-octahydroazuleno[5,6-*b*]oxiren-1a-yl)acrylate (201**)**



To a solution of **144** (50 mg, 0.0834 mmol) in dry benzene (2 mL) was added VO(O^{*i*}Pr)₃ (0.21 μL, 0.000834 mmol, 0.01 equiv) in benzene (0.5 mL) and ^{*t*}BuOOH (22.7 μL, 0.0130 mmol, 1.5 equiv, 5.5M in decane) in benzene (0.5 mL) and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through celite with 80:20 petroleum ether/ethyl acetate and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **201** as a colourless oil (21.0 mg, 41%).

¹H NMR (400 MHz, CDCl₃): δ 7.45-7.28 (m, 5H, Ar), 6.38 (d, 1H, *J* = 0.5 Hz, H-13a), 5.71 (d, 1H, *J* = 0.5 Hz, H-13b), 5.32 (d, 1H, *J* = 12.4 Hz, ArCH¹H²), 5.26 (d, 1H, *J* = 12.4 Hz, ArCH¹H²), 4.82 (s, 1H, H-6), 4.38 (d, 1H, *J* = 7.5 Hz, H-3), 3.16-3.04 (m, 2H, H-1 + H-8), 2.51 (d, 1H, *J* = 0.8 Hz, OH), 2.37 (dd, 1H, *J* = 13.2, 7.1 Hz, H-9a), 2.22 (dd, 1H, *J* = 13.2, 7.7 Hz, H-9b), 2.10 (ddd, 1H, *J* = 14.9, 9.1, 7.9 Hz, H-2a), 1.76-1.70 (m, 1H, H-2b), 1.49 (d, 3H, *J* = 1.7 Hz, H-15), 1.24 (s, 3H, H-14), 0.95 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.87 (s, 9H, CH₃-TBS), 0.58 (q, 6H, *J* = 7.9 Hz, CH₂-TES), 0.07 (s, 3H, CH₃-TBS), 0.05 (s, 3H, CH₃-TBS) ppm.

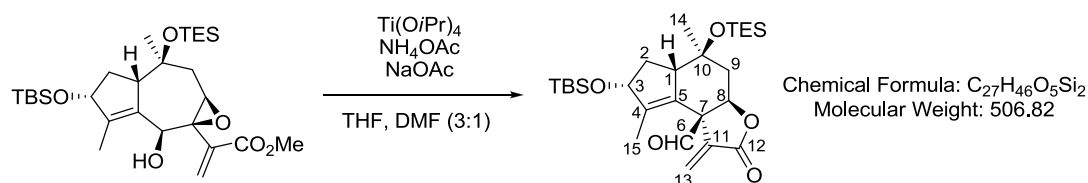
¹³C NMR (101 MHz, CDCl₃): δ 164.8 (C-12), 141.1 (C-4), 138.7 (C-11), 135.65 (C-5), 135.2 (Ar), 129.30 (Ar), 128.65 (Ar), 128.34 (C-13), 128.03 (Ar), 79.3 (C-3), 76.1 (C-10), 66.9 (PhCH₂), 65.7 (C-6), 62.3 (C-7), 58.6 (C-8), 56.6 (C-1), 43.0 (C-9), 34.0 (C-2), 25.8 (Me₃C-TBS), 23.0 (C-14), 18.0 (Me₃C-TBS), 12.7 (C-15), 7.1 (CH₂-TES), 6.8 (CH₃-TES), -4.4 (Me-TBS), -5.0 (Me-TBS) ppm.

IR (thin film): 3401, 2953, 2873, 1726, 1462, 1379, 1255, 1112, 1055, 1001, 835 cm⁻¹.

HRMS (ESI): m/z calculated for $C_{31}H_{56}O_7Si_2$ ($M + Na$)⁺ 637.3357, found 637.3331.

$[\alpha]_D^{25} +23.3$ (c 1.0, $CHCl_3$)

(3a*R*,5*S*,5a*S*,7*R*,8b*R*)-7-(*tert*-Butyldimethylsilyloxy)-5,8-dimethyl-1-methylene-2-oxo-5-(triethylsilyloxy)-2,3a,4,5,5a,6,7,8b-octahydro-1*H*-indeno[5,4-*b*]furan-8b-carbaldehyde (208)



To a solution of epoxide **169** (35.0 mg, 0.0649 mmol) in dry THF (3 mL) was added DMF (1 mL), ammonium acetate (10.0 mg, 0.130 mmol, 2 equiv), sodium acetate (10.7 mg, 0.130 mmol, 2 equiv) and a solution of titanium isopropoxide (38.5 μ L, 0.130 mmol, 2 equiv) in THF (0.5 mL) in that order. The reaction mixture was heated to 70 °C and stirred for 30 minutes. The reaction mixture was allowed to cool to rt and then quenched with saturated aqueous NH_4Cl . The aqueous phase was extracted with ethyl acetate (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/diethyl ether, 90:10) to give **208** as a white crystalline film (5.0 mg, 26%).

1H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H, H-6), 6.54 (s, 1H, H-13a), 5.55 (s, 1H, H-13b), 4.69 (dd, 1H, $J = 11.3, 6.1$ Hz, H-8), 4.62 (t app, 1H, $J = 7.0$ Hz, H-3), 2.52-2.41 (m, 2H, H-1 + H-9a), 2.33 (dt app, 1H, $J = 12.7, 7.3$ Hz, H-2a), 1.67 (dd, 3H, $J = 2.4, 0.9$ Hz, H-15), 1.54-1.51 (m, 1H, H-9b), 1.46 (ddd, 1H, $J = 12.7, 8.6, 7.3$ Hz, H-2b), 1.12 (s, 3H, H-14), 1.00-0.83 (m, 18H, $CH_3-TES + CH_3-TBS$), 0.57 (q, 6H, $J = 7.9$ Hz, CH_2-TES), 0.11 (s, 3H, CH_3-TBS), 0.10 (s, 3H, CH_3-TBS) ppm.

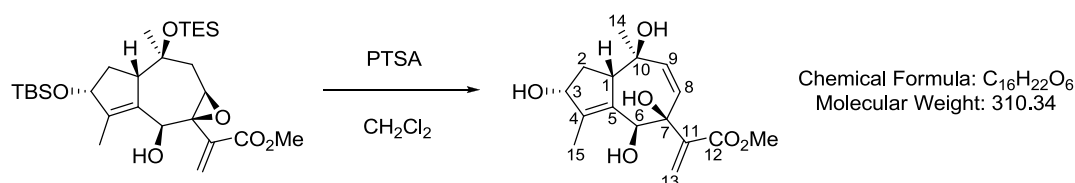
^{13}C NMR (101 MHz, $CDCl_3$): δ 196.1 (C-6), 167.9 (C-12), 143.6 (C-4), 134.1 (C-11), 129.8 (C-5), 125.9 (C-13), 79.4 (C-3), 75.8 (C-8), 72.4 (C-10), 60.5 (C-7), 52.9 (C-1), 45.8 (C-9), 34.2 (C-2), 25.8 (Me_3C-TBS), 22.0 (C-14), 18.1 (Me_3C-TBS), 13.0 (C-15), 7.0 (CH_2-TES), 6.7 (CH_3-TES), -4.3 ($Me-TBS$), -4.8 ($Me-TBS$) ppm.

IR (thin film): 2952, 2870, 1726, 1720, 1455, 1099, 1042, 1003 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{46}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 529.2781, found 529.2753.

$[\alpha]_{\text{D}}^{25}$ -62.9 (c 0.25, CHCl_3)

Methyl 2-((2*R,4*S**,5*S**,8*S**,8*aS**)-2,4,5,8-tetrahydroxy-3,8-dimethyl-1,2,4,5,8,8a-hexahydroazulen-5-yl)acrylate (**211**)**

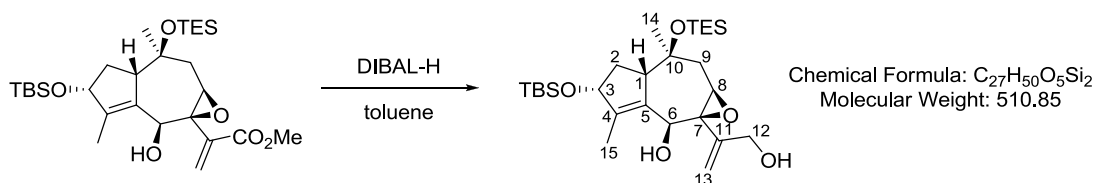


To a solution of epoxide **169** (10.0 mg, 0.0190 mmol) in CH_2Cl_2 (1 mL) was added *p*-TsOH. H_2O (0.64 mg, 0.00370 mmol, 0.2 equiv) at rt. The solution was stirred for 8 h and the reaction quenched with saturated aqueous NaHCO_3 and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 50:50) to give **211** as a colourless oil (4 mg, 40%).

^1H NMR (400 MHz, CDCl_3): δ 6.51 (d, 1H, $J = 5.3$ Hz, H-9), 6.41 (s, 1H, H-13a), 6.32 (d, 1H, $J = 5.3$ Hz, H-8), 5.59 (s, 1H, H-13b), 4.70 (m, 1H, OH), 4.46 (tdd app, 1H, $J = 7.7, 4.8, 1.1$ Hz, H-3), 3.81 (s, 3H, CH_3 ester), 3.63 (d, 1H, $J = 7.8$ Hz, H-6), 3.51-3.41 (m, 1H, H-1), 2.82 (dd, 1H, $J = 18.5, 7.7$ Hz, H-2a), 2.62 (dd, 1H, $J = 18.7, 4.7$ Hz, H-2b), 2.15 (s, 3H, H-15), 1.85 (s, 3H, H-14) ppm.

Further data was not obtained due to rapid degradation of substrate.

(1a*S*,2*S*,4*R*,5a*S*,6*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-1a-(3-hydroxyprop-1-en-2-yl)-3,6-dimethyl-6-(triethylsilyloxy)-1a,2,4,5,5a,6,7,7a-octahydroazuleno[5,6-*b*]oxiren-2-ol (212)



To a solution of epoxide **169** (166 mg, 0.308 mmol) in dry toluene (10 mL) was added dropwise DIBAL-H (1.08 mL, 1.08 mmol, 3.5 equiv, 1 M in hexane) at -78°C and the resulting mixture was stirred for 30 min. The excess DIBAL-H was quenched with ethyl acetate and saturated aqueous NH_4Cl was added. The aqueous phase was extracted with ethyl acetate (x3) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 80:20) to give **212** as a colourless oil (41 mg, 26%).

^1H NMR (400 MHz, CDCl_3): δ 5.27 (d, 1H, $J = 0.5$ Hz, H-13a), 5.18 (d, 1H, $J = 0.5$ Hz, H-13b), 4.80 (s, 1H, H-6), 4.41 (dd, 1H, $J = 7.6, 1.2$ Hz, H-3), 4.20 (d, 2H, $J = 5.5$ Hz, H-12), 3.10 (m, 2H, H-1 + H-8), 2.61 (s, 1H, OH), 2.39 (dd, 1H, $J = 13.2, 7.3$ Hz, H-9a), 2.20–2.09 (m, 2H, H-2a + H-9b), 1.91 (t, 1H, $J = 5.5$ Hz, OH), 1.78–1.69 (m, 1H, H-2a), 1.66 (d, 3H, $J = 1.8$ Hz, H-15), 1.23 (s, 3H, H-14), 0.95 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.88 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.58 (q, 6H, $J = 7.9$ Hz, $\text{CH}_2\text{-TES}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.07 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

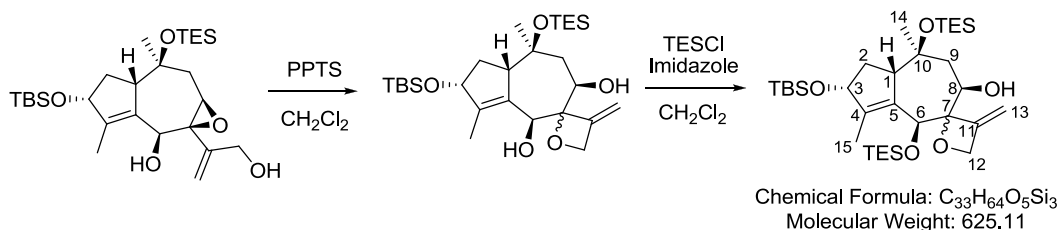
^{13}C NMR (101 MHz, CDCl_3): δ 146.0 (C-4), 141.5 (C-11), 135.6 (C-5), 114.7 (C-13), 79.3 (C-3), 76.2 (C-10), 65.9 (C-7), 63.5 (C-6), 63.4 (C-12), 59.6 (C-1), 56.7 (C-8), 43.1 (C-9), 34.2 (C-2), 25.8 ($\text{Me}_3\text{C-TBS}$), 22.8 (C-14), 18.1 ($\text{Me}_3\text{C-TBS}$), 13.1 (C-15), 7.1 ($\text{CH}_2\text{-TES}$), 6.8 ($\text{CH}_3\text{-TES}$), -4.4 (Me-TBS), -5.0 (Me-TBS) ppm.

IR (thin film): 3417, 2954, 2931, 2877, 1458, 1381, 1249, 1111, 1049, 1002 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{50}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$)⁺ 533.3089, found 533.3064.

$[\alpha]_D^{25}$ +50.7 (c 1.0, CHCl_3)

(2*R,4*S**,6*R**,8*S**,8*aS**)-2-(*tert*-Butyldimethylsilyloxy)-3,8-dimethyl-3'-methylene-4,8-bis(triethylsilyloxy)-2,4,6,7,8,8*a*-hexahydro-1*H*-spiro[azulene-5,2'-oxetan]-6-ol (**214**)**



To a solution of epoxide **212** (27.0 mg, 0.0530 mmol in dry CH₂Cl₂ (5 mL) at rt was added solid *p*-tuenesulfonate (13.3 mg, 0.0530 mmol, 1 equiv). The reaction mixture was stirred at rt for 3 h and the reaction quenched with saturated aqueous NaHCO₃. The aqueous phase was extracted with ethyl acetate (x3) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue (18.4 mg) was redissolved in dry CH₂Cl₂ (2 mL) and imidazole (6.0 mg, 0.0880 mmol, 2.5 equiv) was added followed by the dropwise addition of TESCl (11.0 μL, 0.528 mmol, 2 equiv) at rt. The reaction mixture was stirred at rt for 8 h and the reaction was quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with 1 M aqueous HCl, brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 95:5) to give **214** as a colourless oil (3 mg, 9% over 2 steps).

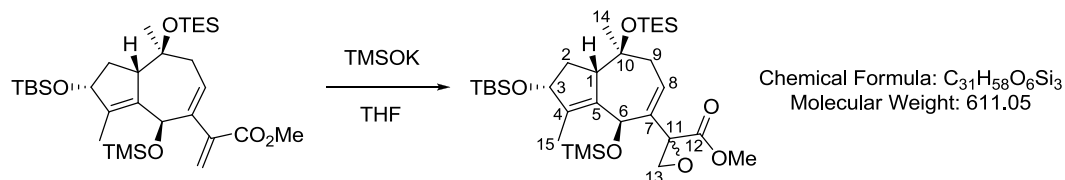
¹H NMR (400 MHz, CDCl₃): δ 5.47 (s, 1H, H-6), 5.31 (br t app, 1H, *J* = 1.9 Hz, H-13a), 5.23 (br t app, 1H, *J* = 2.4 Hz, H-13b), 4.66 (dt app, 1H, *J* = 13.2, 2.3 Hz, H-12a), 4.60 (dt app, 1H, *J* = 13.2, 2.2 Hz, H-12b), 4.50 (d, 1H, *J* = 10.5 Hz, OH), 4.42-4.36 (m, 1H, H-3), 3.79 (ddd, 1H, *J* = 12.8, 10.5, 3.9 Hz, H-8), 2.58-2.51 (m, 1H, H-1), 2.22 (dd, 1H, *J* = 12.0, 3.9 Hz, H-9a), 2.15 (dt, 1H, *J* = 13.7, 8.1 Hz, H-2a), 1.70-1.58 (m, 1H, H-9b), 1.64 (dd, 3H, *J* = 2.0, 0.6 Hz, H-15), 1.45-1.38 (m, 1H, H-2b), 1.17 (s, 3H, H-14), 0.99 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.95 (t, 9H, *J* = 7.9 Hz, CH₃-TES), 0.89 (s, 9H, CH₃-TBS), 0.70 (q, 6H, *J* = 7.9 Hz, CH₂-TES), 0.59 (q, 6H, *J* = 7.8 Hz, CH₂-TES), 0.06 (s, 3H, CH₃-TBS), 0.05 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 146.9 (C-4), 139.4 (C-11), 134.1 (C-5), 107.9 (C-7), 105.2 (C-13), 80.9 (C-3), 76.9 (C-10), 74.1 (C-6), 71.7 (C-12), 71.4 (C-8), 58.7 (C-1), 49.5 (C-9), 32.1 (C-2), 25.9 (Me₃C-TBS), 23.1 (C-14), 18.2 (Me₃C-TBS), 11.9 (H-15), 7.1 (CH₂-TES), 6.8 (CH₂-TES), 6.7 (CH₃-TES), 4.7 (CH₃-TES), -4.4 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 2952, 2860, 1448, 1223, 1110, 1053, 1003 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{33}\text{H}_{64}\text{O}_5\text{Si}_3$ ($\text{M} + \text{Na}$) $^{+}$ 647.3959, found 647.3925.

Methyl 2-((2*R,4*S**,8*S**,8*aS**)-2-(*tert*-butyldimethylsilyloxy)-3,8-dimethyl-8-(triethylsilyloxy)-4-(trimethylsilyloxy)-1,2,4,7,8,8*a*-hexahydroazulen-5-yl)oxirane-2-carboxylate (**216**)**



To a solution of ester **139** (30.0 mg, 0.170 mmol) in dry THF (5 mL) was added TMSOK (14.3 mg, 0.370 mmol, 2.2 equiv, 80% technical grade) at room temperature and the reaction was stirred for 1 h. Water was added to the reaction mixture, and adjusted the pH 2 by the addition of 0.1 M aqueous HCl. The aqueous layer was extracted with ethyl acetate (5x) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **216** as a colourless oil (14.6 mg, 48%, dr 1.7:1).

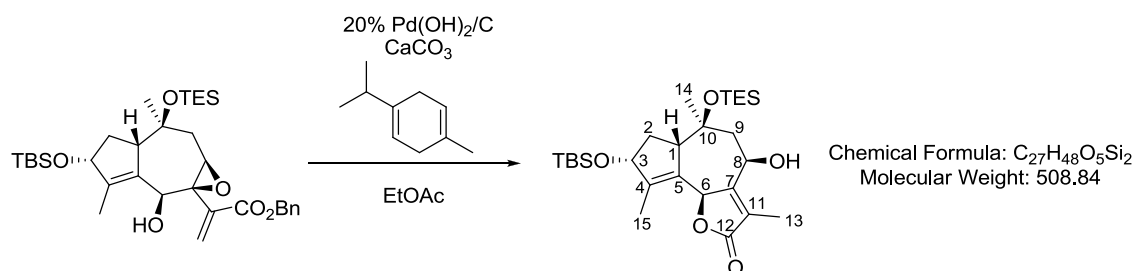
^1H NMR (400 MHz, CDCl_3): δ 6.01-5.88 (m, 1H, H-8), 4.90 (d, 1H, $J = 1.1$ Hz, H-6), 4.46-4.33 (m, 1H, H-3), 3.73 (s, 3H, COOMe), 3.31-3.11 (m, 3H, H-1 + H-13a + H-9a), 2.79 (d, 1H, $J = 6.5$ Hz, H-13b), 2.26-2.02 (m, 2H, H-2a + H-9b), 1.77-1.68 (m, 1H, H-2b), 1.58 (d, 3H, $J = 1.9$ Hz, H-15), 1.01 (s, 3H, H-14), 0.95 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.88 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.58 (q, 6H, $J = 8.0$ Hz, $\text{CH}_2\text{-TES}$), 0.10-0.00 (m, 15H, $\text{CH}_3\text{-TBS}$ + $\text{CH}_3\text{-TMS}$) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 169.8 (C-12), 137.8 (C-4), 136.8 (C-5), 135.5 (C-7), 131.3 (C-8), 79.5 (C-3), 76.6 (C-10), 67.3 (C-6), 59.5 (C-11), 57.9 (C-1), 53.3 (C-13), 52.8 (COOMe), 41.4 (C-9), 34.3 (C-2), 25.8 ($\text{Me}_3\text{C-TBS}$), 22.0 (C-14), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.0 (C-15), 7.2 ($\text{CH}_2\text{-TES}$), 6.9 ($\text{CH}_3\text{-TES}$), 0.0 (Me-TMS), -4.4 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2954, 2877, 1751, 1249, 1111, 1040, 1010 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{31}\text{H}_{58}\text{O}_6\text{Si}_3$ ($\text{M} + \text{Na}$)⁺ 633.3438, found 633.3399.

(4*R*,6*S*,6*aS*,8*R*,9*bS*)-8-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-3,6,9-trimethyl-6-(triethylsilyloxy)-4,5,6,6*a*,7,8-hexahydroazuleno[4,5-*b*]furan-2(9*bH*)-one (218)



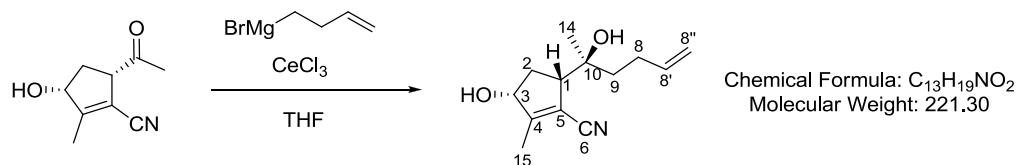
To a solution of epoxide **201** (20 mg, 0.033 mmol) in EtOAc (0.5 mL) and γ -terpinene (0.5 mL) was added calcium carbonate (32 mg, 0.325 mmol, 10 equiv) and 20% $\text{Pd}(\text{OH})_2/\text{C}$ (16 mg). The reaction mixture was heated to 70 $^\circ\text{C}$ and stirred for 2.5 h. The reaction was cooled down to rt and the solids filtered off. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/diethyl ether, 50:50) to give **218** as a colourless oil (10 mg, 60%).

^1H NMR (400 MHz, CDCl_3): δ 5.48 (s, 1H, H-6), 4.55 (br s, 1H, H-8), 4.41 (d, 1H, $J = 8.0$ Hz, H-3), 2.71-2.58 (m, 1H, H-1), 2.16 (dt app, 1H, $J = 15.1, 8.6$ Hz, H-2*a*), 2.11-1.98 (m, 5H, H-9 + H-13), 1.82 (m, 4H, H-15 + H-2*b*), 1.20 (s, 3H, H-14), 0.95 (t, 9H, $J = 7.9$ Hz, $\text{CH}_3\text{-TES}$), 0.89 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.60 (q, 6H, $J = 7.9$ Hz, $\text{CH}_2\text{-TES}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ 174.8 (C-12), 162.0 (C-7), 141.2 (C-4), 131.0 (C-5), 128.0 (C-11), 78.0 (C-3), 78.0 (C-6), 77.6 (C-10), 67.1 (C-8), 55.5 (C-1), 34.3 (C-9), 29.6 (C-2), 25.8 ($\text{Me}_3\text{C-TBS}$), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.6 (C-15), 9.5 (C-13), 7.1 ($\text{CH}_2\text{-TES}$), 6.8 ($\text{CH}_3\text{-TES}$), -4.6 (Me-*TBS*), -4.9 (Me-*TBS*) ppm.

IR (thin film): 3453, 2958, 2870, 1763, 1249, 1109, 1048, 1005 cm^{-1} .

(3*R*,5*S*)-3-Hydroxy-5-((*S*)-2-hydroxyhex-5-en-2-yl)-2-methylcyclopent-1-enecarbonitrile (221**)**



CeCl₃·7H₂O (3.90 g, 10.5 mmol, 2.2 equiv) was dried under vacuum at 60 °C (4h), 80 °C (4h), 100 °C (12h), 140 °C (4h), in that order. Dry THF (70 mL) was added and the white suspension was sonicated for 1 h. The suspension was then cooled to -78 °C and but-3-enylmagnesium bromide (13.1 mL, 10.5 mmol, 2.2 equiv, 0.8 M in THF) was added dropwise. The resulting solution was stirred for 1 h at -78 °C, after which a solution of ketone **84** (786 mg, 4.76 mmol) in dry THF (5 mL) was added dropwise and the reaction mixture was left to stir for 1 h. The reaction was quenched with saturated aqueous NH₄Cl, diluted with brine and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 60:40 up to 40:60) to give **221** as a yellow oil (320 mg, 30% over 2 steps, dr 2.3:1).

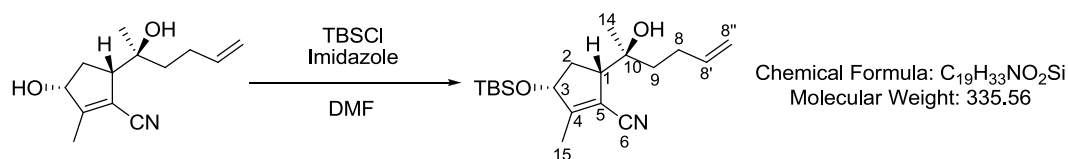
¹H NMR (400 MHz, CDCl₃): δ 5.98-5.74 (m, 1H, H-8''), 5.16-4.94 (m, 2H, H-8'), 4.40-4.28 (m, 1H, H-3), 3.58-3.32 (m, 1H, OH), 2.90-2.79 (m, 1H, H-1), 2.37-2.20 (m, 1H, H-2a), 2.19-2.11 (m, 1H, H-2b), 2.10 (d, 3H, *J* = 1.7 Hz, H-15), 1.99 – 1.71 (m, 3H, H-8 + H-9a), 1.70 – 1.63 (m, 1H, H-9b) 1.46 (s, 3H, H-14) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 164.4 (C-4), 138.0 (C-8'), 117.6 (C-6), 115.3 (C-8''), 111.1 (C-5), 76.9 (C-10), 73.3 (C-3), 54.2 (C-1), 40.6 (C-9), 34.9 (C-8), 28.5 (C-14), 25.7 (C-2), 14.6 (C-15) ppm.

IR (thin film): 3398, 2974, 2941, 1639, 1438, 1379, 1161, 1039, 912 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₃H₁₉NO₂ (M + Na)⁺ 244.1308, found 244.1309.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-((*S*)-2-hydroxyhex-5-en-2-yl)-2-methylcyclopent-1-enecarbonitrile (223**)**



To a solution of diol **221** (320 mg, 1.45 mmol) in dry DMF (10 mL) was added imidazole (381 mg, 5.60 mmol, 4 equiv) and TBDMSCl (436 mg, 2.80 mmol, 2 equiv). The reaction mixture was heated to 40 °C and stirred overnight. The reaction was quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with 1 M aqueous HCl, brine (x4), dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting diastereomeric mixture was inseparable during column chromatography thus **223** was obtained as a crude colourless oil (487 mg) and used directly in the next step.

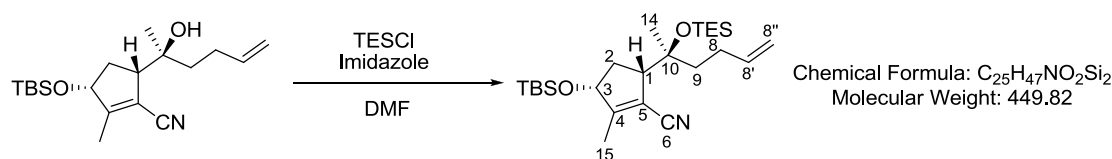
¹H NMR (400 MHz, CDCl₃): δ 5.87-5.64 (m, 1H, H-8'), 5.01-4.93 (m, 1H, H-8''a), 4.91-4.85 (m, 1H, H-8''b), 4.53-4.37 (m, 1H, H-3), 2.84-2.72 (m, 1H, H-1), 2.28-1.97 (m, 3H, H-2 + H-8a), 1.92-1.88 (m, 3H, H-15), 1.62-1.34 (m, 3H, H-8b + H-9), 1.19 (s, 3H, H-14), 0.80 (s, 9H, CH₃-TBS), 0.00 (s, 6H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 163.3 (C-4), 138.7 (C-8'), 117.3 (C-6), 114.9 (C-8''), 111.3 (C-5), 77.4 (C-10), 73.2 (C-3), 54.4 (C-1), 39.3 (C-9), 35.7 (C-8), 28.2 (C-14), 25.7 (C-2), 25.7 (Me₃C-TBS), 18.0 (Me₃C-TBS), 14.6 (C-15), -3.6 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 3468, 2931, 2858, 1639, 1462, 1438, 1357, 1253, 1099, 1053, 906, 894, 837, 775 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₁₉H₃₃NO₂Si (M + Na)⁺ 358.2173, found 358.2163.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-((*S*)-2-(triethylsilyloxy)hex-5-en-2-yl)cyclopent-1-enecarbonitrile (224**)**



To a solution of alcohol **223** (487 mg, 1.45 mmol) in dry DMF (20 mL) was added imidazole (987 mg, 14.5 mmol, 10 equiv) and TESCl (1.22 mL, 7.25 mmol, 5 equiv). The reaction was heated to 80 °C and stirred for 24 h. The reaction was quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with 1 M aqueous HCl, brine (x4), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 99:1) to give **224** as a colourless oil (554 mg, 85% over 2 steps, dr 2.3:1).

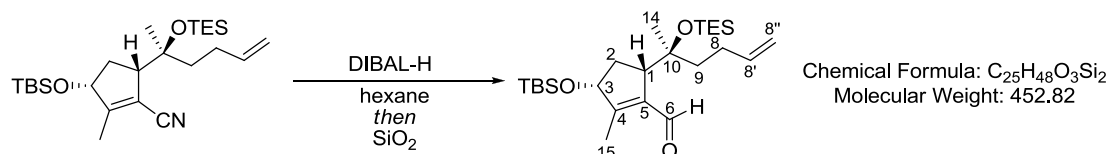
¹H NMR (400 MHz, CDCl₃): δ 5.83-5.68 (m, 1H, H-8'), 4.96 (ddd, 1H, *J* = 17.1, 3.4, 1.6 Hz, H-8''a), 4.92-4.82 (m, 1H, H-8''b), 4.54-4.36 (m, 1H, H-3), 2.86-2.72 (m, 1H, H-1), 2.26-2.15 (m, 1H, H-2a), 2.15-1.95 (m, 2H, H-2b + H-9a) 1.88 (dd, 3H, *J* = 2.3, 1.1 Hz, H-15), 1.69-1.40 (m, 3H, H-9b, + H-8), 1.21 (s, 3H, H-14), 0.93-0.84 (m, 9H, CH₃-TES), 0.82 (s, 9H, CH₃-TBS), 0.62-0.49 (m, 6H, CH₂-TES), 0.01 (s, 3H, CH₃-TBS), 0.00 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 163.8 (C-4), 138.8 (C-8'), 117.2 (C-6), 114.4 (C-8''), 110.9 (C-5), 77.4 (C-3), 73.2 (C-10), 53.6 (C-1), 39.5 (C-9), 36.0 (C-8), 28.4 (C-14), 25.7 (Me₃C-TBS), 25.6 (C-2), 18.0 (Me₃C-TBS), 14.2 (C-15), 7.2 (CH₂-TES), 6.9 (CH₃-TES), -4.5 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2947, 2877, 1643, 1458, 1357, 1249, 1056, 1002, 902 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₅H₄₇NO₂Si₂ (M + Na)⁺ 472.3038, found 472.3031.

(3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-((*S*)-2-(triethylsilyloxy)hex-5-en-2-yl)cyclopent-1-enecarbaldehyde (225**)**



To a solution of nitrile **224** (200 mg, 0.445 mmol) in dry hexane (20 mL) at -78 °C was added dropwise a solution of DIBAL-H (0.670 mL, 0.670 mmol, 1.5 equiv, 1 M in hexane). The reaction mixture was warmed to 0 °C for 20 min then cooled back down to -78 °C. Ethyl acetate (1 mL) was added to quench the excess DIBAL-H and the reaction mixture was left to stir for 10 min, after which SiO₂ (10g) was added and the temperature raised to rt and stirring maintained for a further 4 h. The reaction was filtered and concentrated *in vacuo* to give crude aldehyde **225** as a colourless oil (206 mg). The residue was determined to be pure enough by NMR to continue without further purification.

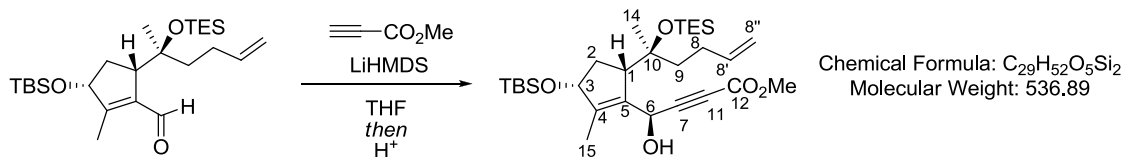
¹H NMR (400 MHz, CDCl₃): δ 9.92 (s, 1H, H-6), 5.90-5.71 (m, 1H, H-8'), 5.10-4.83 (m, 2H, H-8''), 4.50-4.43 (m, 1H, H-3), 3.24-3.06 (m, 1H, H-1), 2.33-2.03 (m, 3H, H-2 + H-9a), 2.04-1.99 (m, 3H, H-15), 1.65-1.37 (m, 3H, H-9b + H-8''), 1.19 (s, 3H, H-14), 0.94-0.90 (m, 9H, CH₃-TES), 0.89 (s, 9H, CH₃-TBS), 0.68-0.56 (m, 6H, CH₂-TES), 0.10 (s, 3H, CH₃-TBS), 0.09 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 192.6 (C-6), 157.4 (C-4), 139.3 (C-8'), 137.6 (C-5), 114.0 (C-8''), 78.6 (C-3), 77.7 (C-10), 53.6 (C-1), 38.8 (C-9), 35.3 (C-8), 28.4 (C-14), 26.5 (C-2), 25.8 (Me₃C-TBS), 18.1 (Me₃C-TBS), 13.1 (C-15), 6.8 (CH₂-TES), 6.4 (CH₃-TES), -4.5 (Me-TBS), -4.9 (Me-TBS) ppm.

IR (thin film): 2931, 2877, 1681, 1635, 1458, 1373, 1249, 1149, 1064, 1002 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₂₅H₄₈O₃Si₂ (M + Na)⁺ 475.3034, found 475.3014.

(R)-Methyl 4-((3R,5S)-3-(tert-butyldimethylsilyloxy)-2-methyl-5-((S)-2-(triethylsilyloxy)hex-5-en-2-yl)cyclopent-1-enyl)-4-hydroxybut-2-ynoate (226)



$CeCl_3 \cdot 7H_2O$ (497 mg, 1.34 mmol, 3 equiv) was dried under vacuum at 60 °C (4 h), 80 °C (4 h), 100 °C (12 h), 140 °C (4 h), in that order. Dry THF (20 mL) was added and the white suspension was sonicated for 1 h and then cooled to -78 °C. To a separate solution of HMDS (281 μ L, 1.34 mmol, 3 equiv) in dry THF (5 mL) at 0 °C was added dropwise a solution of n BuLi (536 μ L, 1.34 mmol, 3 equiv, 2.5 M in hexanes), stirred for 5 min and transferred *via* cannula to the reaction mixture. Methyl propiolate (120 μ L, 1.34 mmol, 3 equiv) was added dropwise and after stirring at -78 °C for 10 min, crude aldehyde **225** (206 mg, 0.446 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl , diluted with brine and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 97:3) to give **226** as a colourless oil (141 mg, 59%, dr >20:1), followed by C-10 epimer **227** as a colourless oil (42 mg, 18%, dr >20:1).

1H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddt app, 1H, J = 16.9, 10.2, 6.5 Hz, H-8'), 5.25 (d, 1H, J = 9.2 Hz, H-6), 5.00-4.93 (m, 1H, H-8''a), 4.92-4.84 (m, 1H, H-8''b), 4.74 (d, 1H, J = 9.3 Hz, OH), 4.39 (dd, 1H, J = 7.3, 4.6 Hz, H-3), 3.73 (s, 3H, COOMe), 2.92 (t app, 1H, J = 6.3 Hz, H-1), 2.35-2.13 (m, 2H, H-2a + H-8a), 2.12-1.99 (m, 1H, H-2b), 1.91-1.80 (m, 1H, H-8b), 1.74 (d, 3H, J = 1.4 Hz, H-15), 1.61 (ddd, 1H, J = 14.3, 12.5, 4.7 Hz, H-9a), 1.32-1.22 (m, 4H, H-9b + H-14), 0.98 (t, 9H, J = 7.9 Hz, CH_3 -TES), 0.87 (s, 9H, CH_3 -TBS), 0.71 (q, 6H, J = 7.9 Hz, CH_2 -TES), 0.06 (s, 3H, CH_3 -TBS), 0.04 (s, 3H, CH_3 -TBS) ppm.

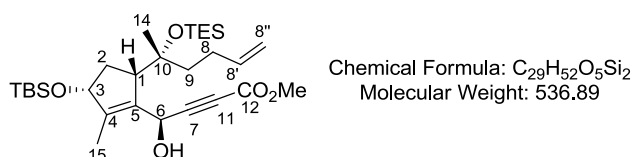
^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (C-12), 142.4 (C-4), 138.9 (C-5), 135.3 (C-8'), 114.0 (C-8''), 87.8 (C-7), 80.1 (C-11), 78.2 (C-3), 76.1 (C-10), 59.5 (COOMe), 57.4 (C-1), 52.5 (C-6), 36.7 (C-8), 36.3 (C-9), 28.6 (C-14), 26.4 (C-2), 25.8 (Me_3C -TBS), 18.1 (Me_3C -TBS), 12.5 (C-15), 7.0 (CH_2 -TES), 6.9 (CH_3 -TES), -4.5 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 3362, 2954, 2877, 1718, 1434, 1378, 1360, 1243, 1003 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{29}\text{H}_{52}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$)⁺ 559.3245, found 559.3235.

$[\alpha]_{\text{D}}^{25}$ -6.91 (c 1.0, CHCl_3)

(*R*)-Methyl 4-((3*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-((*R*)-2-(triethylsilyloxy)hex-5-en-2-yl)cyclopent-1-enyl)-4-hydroxybut-2-ynoate (227)



^1H NMR (400 MHz, CDCl_3): δ 5.83 (ddt app, 1H, J = 16.7, 10.2, 6.4 Hz, H-8'), 5.39 (d, 1H, J = 11.1 Hz, H-6), 5.21 (d, 1H, J = 11.1 Hz, OH), 5.13-4.95 (m, 2H, H-8''), 4.44 (dd, 1H, J = 7.9, 2.7 Hz, H-3), 3.78 (s, 3H, COOMe), 3.17-3.04 (m, 1H, H-1), 2.38-2.19 (m, 2H, H-2a + H-8a), 2.10 (m, 1H, H-8b), 1.76-1.69 (m, 3H, H-15), 1.69-1.57 (m, 2H, H-2b + H-9a), 1.34 (s, 3H, H-14), 1.24 (ddd, 1H, J = 14.1, 4.4, 3.3 Hz, H-9b), 1.02 (t, 9H J = 7.9 Hz, $\text{CH}_3\text{-TES}$), 0.91 (s, 9H, $\text{CH}_3\text{-TBS}$), 0.85 – 0.74 (m, 6H, $\text{CH}_2\text{-TES}$), 0.10 (s, 3H, $\text{CH}_3\text{-TBS}$), 0.08 (s, 3H, $\text{CH}_3\text{-TBS}$) ppm.

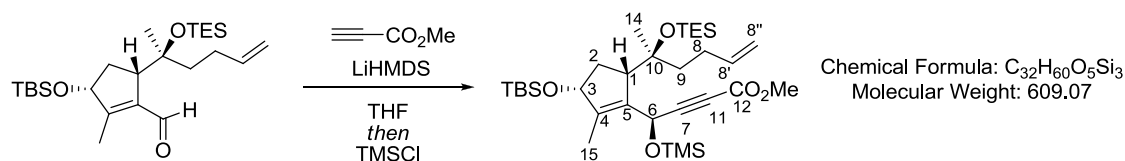
^{13}C NMR (101 MHz, CDCl_3): δ 154.0 (C-12), 140.5 (C-4), 138.1 (C-5), 135.9 (C-8'), 114.6 (C-8''), 88.0 (C-7), 80.4 (C-11), 78.7 (C-3), 75.8 (C-10), 59.5 (COOMe), 52.5 (C-1), 51.8 (C-6), 40.4 (C-8), 36.0 (C-9), 27.4 (C-14), 25.8 ($\text{Me}_3\text{C-TBS}$), 25.2 (C-2), 18.1 ($\text{Me}_3\text{C-TBS}$), 12.4 (C-15), 7.02 ($\text{CH}_2\text{-TES}$), 6.6 ($\text{CH}_3\text{-TES}$), -4.5 (Me-TBS), -4.7 (Me-TBS) ppm.

IR (thin film): 3361, 2956, 2878, 1717, 1434, 1247, 1004 cm^{-1} .

HRMS (ESI): m/z calculated for $\text{C}_{29}\text{H}_{52}\text{O}_5\text{Si}_2$ ($\text{M} + \text{Na}$)⁺ 559.3245, found 559.3231.

$[\alpha]_{\text{D}}^{25}$ -4.72 (c 1.0, CHCl_3)

(R)-Methyl 4-((3R,5S)-3-(tert-butyldimethylsilyloxy)-2-methyl-5-((S)-2-(triethylsilyloxy)hex-5-en-2-yl)cyclopent-1-enyl)-4-(trimethylsilyloxy)but-2-ynoate (228)



To a solution of methyl propiolate (45 μ L, 0.507 mmol, 3 equiv) in dry THF (5 mL) at -78°C was added dropwise a solution of LiHMDS (0.507 mmol, 3 equiv) in dry THF (5 mL). After stirring at -78°C for 10 min, aldehyde **225** (76.5 mg, 0.169 mmol) in dry THF (2 mL) was added dropwise to the reaction mixture and stirred at -78°C for 1 h. TMSCl (210 μ L, 1.69 mmol, 10 equiv) was added dropwise and the reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction was then quenched with saturated aqueous NaHCO₃ and the aqueous phase was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/diethyl ether, 99:1) to give **228** as a colourless oil (83 mg, 81%, dr 2.3:1).

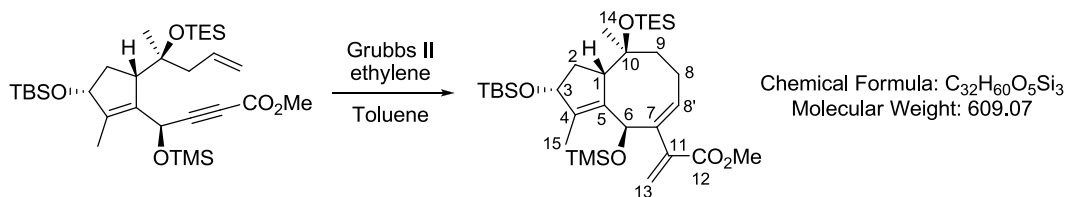
¹H NMR (400 MHz, CDCl₃): δ 5.92-5.72 (m, 1H, H-8' + H-6), 5.08-4.86 (m, 2H, H-8''), 4.44-4.32 (m, 1H, H-3), 3.75 (s, 3H, COOMe), 2.88-2.69 (m, 1H, H-1), 2.32-1.99 (m, 3H, H-2a + H-8), 1.85 (d, 3H, $J = 1.3$ Hz, H-15), 1.65-1.39 (m, 2H, H-2b + H-9a), 1.33-1.10 (m, 4H, H-14 + H-9b), 0.99 (t, 9H, $J = 6.8$ Hz, CH₃-TES), 0.90 (s, 9H, CH₃-TBS), 0.74-0.57 (m, 3H, CH₂-TES), 0.18 (s, 9H, CH₃-TMS), 0.08 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 154.0 (C-12), 143.7 (C-4), 139.3 (C-5), 134.8 (C-8'), 114.0 (C-8''), 88.8 (C-7), 78.7 (C-11), 78.2 (C-3), 75.7 (C-10), 60.1 (COOMe), 55.2 (C-1), 52.4 (C-6), 37.0 (C-8), 36.2 (C-9), 28.2 (C-14), 26.1 (C-2), 25.8 (Me₃C-TBS), 18.1 (Me₃C-TBS), 12.6 (C-15), 7.3 (CH₂-TES), 7.0 (CH₃-TES), 0.01 (Me-TMS) -4.5 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 2953, 2875, 1720, 1433, 1249, 1078, 839 cm⁻¹.

HRMS (ESI): m/z calculated for C₃₃H₆₀O₅Si₃ (M + Na)⁺ 631.3646, found 631.3633.

Methyl 2-((2*R*,4*S*,9*S*,9*aS*,*Z*)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,9-dimethyl-9-(triethylsilyloxy)-2,4,7,8,9,9*a*-hexahydro-1*H*-cyclopenta[8]annulen-5-yl)acrylate (230**)**



After following the general RCEYM procedure with enyne **228** (20 mg, 0.0328 mmol) the crude residue was purified by flash column chromatography (petroleum ether/diethyl ether, 99:1) to give **230** as a colourless oil (15.4 mg, 77%, dr 5:1).

¹H NMR (400 MHz, CDCl₃): δ 5.88 (d, 1H, *J* = 1.9 Hz, H-13a), 5.69 (t app, 1H, *J* = 7.1 Hz, H-8'), 5.47 (s, 1H, H-6), 5.44 (d, 1H, *J* = 1.9 Hz, H-13b), 4.26 (t app, 1H, *J* = 6.2 Hz, H-3), 3.67 (s, 3H, COOMe), 2.75 (br t app, 1H, *J* = 7.1 Hz, H-1), 2.53-2.36 (m, 1H, H-2a), 2.31-2.15 (m, 2H, H-8), 2.06-1.92 (m, 1H, H-2b), 1.79 (s, 3H, H-15), 1.74 – 1.58 (m, 2H, H-9), 1.19 (s, 3H, H-14), 0.94 (t, 9H, *J* = 8.0 Hz, CH₃-TES), 0.90 (s, 9H, CH₃-TBS), 0.57 (q, 6H, *J* = 8.0 Hz, CH₂-TES), 0.11-0.03 (m, 15H, CH₃-TBS + CH₃-TMS) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 168.2 (C-12), 139.7 (C-4), 139.0 (C-11), 135.9 (C-7), 129.1 (C-5), 129.0 (C-8'), 124.1 (C-13), 78.4 (C-3), 77.2 (C-10), 70.8 (C-6), 53.8 (C-1), 51.7 (COOMe), 42.1 (C-9), 34.3 (C-8), 29.7 (C-9), 25.9 (Me₃C-TBS), 25.8 (C-14), 24.6 (C-2), 18.2 (Me₃C-TBS), 12.8 (C-15), 7.2 (CH₂-TES), 7.0 (CH₃-TES), 0.3 (Me-TMS), -4.4 (Me-TBS), -4.8 (Me-TBS) ppm.

IR (thin film): 2951, 2873, 1734, 1666, 1325, 1249, 1099, 887, 837, 773, 742 cm⁻¹.

HRMS (ESI): *m/z* calculated for C₃₃H₆₀O₅Si₃ (M + Na)⁺ 631.3646, found 631.3626.

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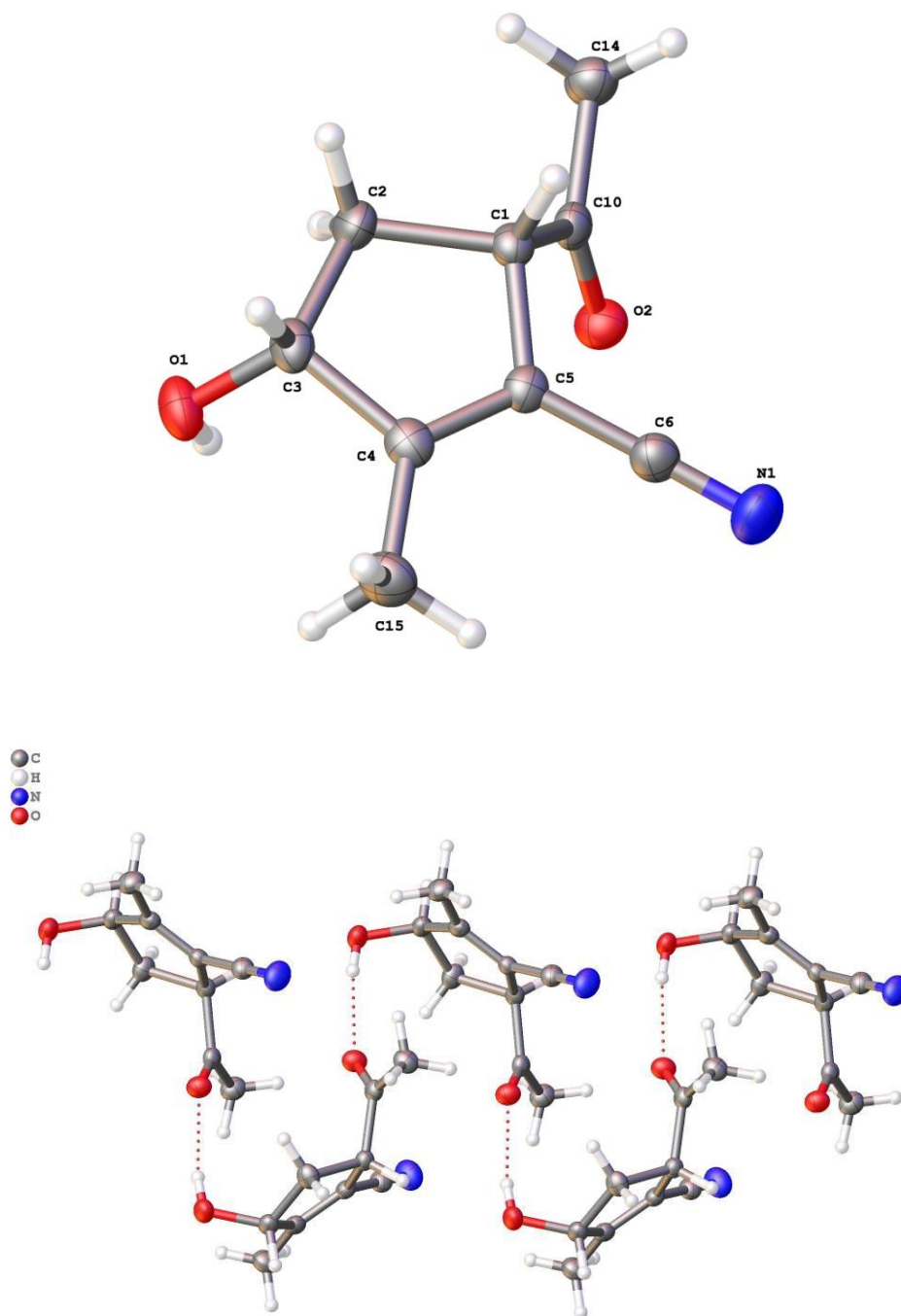
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Appendix A



Views showing the structure and atom labelling scheme of **84**, above, and hydrogen bonding interactions below. Atomic displacement ellipsoids drawn at 50% probability level.

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1.

Computing details

Data collection: *APEX3* Ver. 2016.9-0 (Bruker-AXS, 2016); cell refinement: *SAINT* V8.37A (Bruker-AXS, 2016); data reduction: *APEX3* Ver. 2016.9-0 (Bruker-AXS, 2016); program(s) used to solve structure: *SHELXT* 2014/5 (Sheldrick, 2014); program(s) used to refine structure: *SHELXL* (Sheldrick, 2015); molecular graphics: *Olex2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *Olex2* (Dolomanov *et al.*, 2009).

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Crystal data

$\text{C}_9\text{H}_{11}\text{NO}_2$	$D_x = 1.267 \text{ Mg m}^{-3}$
$M_r = 165.19$	Cu $K\alpha$ radiation, $\lambda = 1.54178 \text{ \AA}$
Orthorhombic, $P2_12_12_1$	Cell parameters from 9509 reflections
$a = 6.6747 (12) \text{ \AA}$	$\theta = 3.2\text{--}68.3^\circ$
$b = 9.2458 (16) \text{ \AA}$	$\mu = 0.74 \text{ mm}^{-1}$
$c = 14.037 (2) \text{ \AA}$	$T = 150 \text{ K}$
$V = 866.3 (3) \text{ \AA}^3$	Block, colourless
$Z = 4$	$0.26 \times 0.24 \times 0.16 \text{ mm}$
$F(000) = 352$	

Data collection

Bruker D8 VENTURE diffractometer	1564 independent reflections
Radiation source: microfocus sealed tube, INCOATEC I μ s 3.0	1563 reflections with $I > 2\sigma(I)$
Multilayer mirror optics monochromator	$R_{\text{int}} = 0.036$
Detector resolution: $7.4074 \text{ pixels mm}^{-1}$	$\theta_{\text{max}} = 68.3^\circ$, $\theta_{\text{min}} = 5.7^\circ$
ϕ and ω scans	$h = -8 \rightarrow 8$
Absorption correction: multi-scan <i>SADABS2016/2</i> (Bruker, 2016/2) was used for absorption correction. $wR2(\text{int})$ was 0.1111 before and 0.0529 after correction. The Ratio of minimum to maximum transmission is 0.6795. The $\lambda/2$ correction factor is Not present.	$k = -11 \rightarrow 11$
$T_{\text{min}} = 0.512$, $T_{\text{max}} = 0.753$	$l = -16 \rightarrow 16$
19408 measured reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained

$R[F^2 > 2\sigma(F^2)] = 0.027$	$w = 1/[\sigma^2(F_o^2) + (0.033P)^2 + 0.1846P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.069$	$(\Delta/\sigma)_{\max} < 0.001$
$S = 1.10$	$\Delta_{\max} = 0.16 \text{ e } \text{\AA}^{-3}$
1564 reflections	$\Delta_{\min} = -0.12 \text{ e } \text{\AA}^{-3}$
112 parameters	Absolute structure: Flack x determined using 633 quotients $[(I+)-(I-)]/[(I+)+(I-)]$ (<i>Acta Cryst.</i> 2013 , B69, 249).
0 restraints	Absolute structure parameter: -0.01 (4)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.91653 (18)	0.41443 (13)	0.47119 (9)	0.0312 (3)
H1	0.934434	0.500184	0.489028	0.047*
O2	0.42929 (18)	0.78354 (12)	0.49417 (8)	0.0275 (3)
N1	0.2144 (3)	0.5694 (2)	0.68998 (11)	0.0385 (4)
C1	0.4020 (2)	0.53656 (16)	0.44821 (11)	0.0210 (3)
H1A	0.281256	0.483954	0.424190	0.025*
C2	0.5934 (3)	0.48161 (19)	0.39573 (12)	0.0272 (4)
H2A	0.556026	0.425541	0.338340	0.033*
H2B	0.677993	0.564259	0.375903	0.033*
C3	0.7075 (3)	0.38482 (18)	0.46705 (12)	0.0251 (4)
H3	0.688144	0.281350	0.448451	0.030*
C4	0.6047 (2)	0.41065 (16)	0.56131 (12)	0.0235 (3)
C5	0.4437 (2)	0.49434 (16)	0.55024 (11)	0.0210 (3)
C6	0.3153 (3)	0.53655 (18)	0.62739 (11)	0.0259 (4)
C10	0.3770 (2)	0.69812 (18)	0.43305 (11)	0.0215 (3)
C14	0.2905 (3)	0.74386 (19)	0.33954 (12)	0.0295 (4)
H14A	0.145312	0.728226	0.340072	0.044*
H14B	0.350993	0.686676	0.288271	0.044*
H14C	0.318609	0.846651	0.328984	0.044*
C15	0.6830 (3)	0.3463 (2)	0.65123 (13)	0.0333 (4)
H15A	0.826510	0.367060	0.656895	0.050*
H15B	0.662259	0.241378	0.650211	0.050*
H15C	0.611809	0.388122	0.705706	0.050*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0208 (6)	0.0266 (6)	0.0464 (7)	0.0028 (5)	0.0020 (5)	-0.0048 (5)
O2	0.0319 (7)	0.0231 (6)	0.0276 (6)	0.0009 (5)	-0.0014 (5)	-0.0035 (5)
N1	0.0379 (9)	0.0481 (9)	0.0296 (8)	0.0077 (8)	0.0088 (7)	0.0018 (7)
C1	0.0190 (7)	0.0211 (7)	0.0228 (7)	-0.0007 (6)	-0.0006 (6)	-0.0030 (6)
C2	0.0264 (8)	0.0309 (8)	0.0243 (7)	0.0049 (8)	0.0026 (7)	-0.0050 (7)
C3	0.0224 (8)	0.0195 (8)	0.0334 (9)	0.0008 (7)	0.0012 (7)	-0.0052 (7)
C4	0.0241 (8)	0.0174 (7)	0.0291 (8)	-0.0025 (7)	-0.0017 (7)	-0.0012 (6)
C5	0.0206 (8)	0.0186 (7)	0.0237 (7)	-0.0031 (6)	0.0018 (6)	-0.0009 (6)
C6	0.0263 (8)	0.0263 (8)	0.0252 (8)	0.0007 (7)	-0.0001 (7)	0.0029 (7)

C10	0.0173 (7)	0.0242 (8)	0.0232 (7)	0.0006 (6)	0.0038 (6)	-0.0021 (6)
C14	0.0329 (9)	0.0305 (9)	0.0252 (8)	0.0037 (8)	-0.0007 (7)	0.0014 (7)
C15	0.0363 (10)	0.0289 (9)	0.0346 (9)	0.0042 (8)	-0.0048 (9)	0.0035 (7)

Geometric parameters (Å, °)

O1—H1	0.8400	C3—C4	1.509 (2)
O1—C3	1.423 (2)	C4—C5	1.333 (2)
O2—C10	1.217 (2)	C4—C15	1.490 (2)
N1—C6	1.148 (2)	C5—C6	1.435 (2)
C1—H1A	1.0000	C10—C14	1.495 (2)
C1—C2	1.560 (2)	C14—H14A	0.9800
C1—C5	1.510 (2)	C14—H14B	0.9800
C1—C10	1.518 (2)	C14—H14C	0.9800
C2—H2A	0.9900	C15—H15A	0.9800
C2—H2B	0.9900	C15—H15B	0.9800
C2—C3	1.544 (2)	C15—H15C	0.9800
C3—H3	1.0000		
C3—O1—H1	109.5	C15—C4—C3	121.33 (14)
C2—C1—H1A	110.0	C4—C5—C1	114.14 (14)
C5—C1—H1A	110.0	C4—C5—C6	123.45 (15)
C5—C1—C2	102.29 (13)	C6—C5—C1	122.37 (14)
C5—C1—C10	114.05 (12)	N1—C6—C5	179.06 (18)
C10—C1—H1A	110.0	O2—C10—C1	120.53 (15)
C10—C1—C2	110.15 (13)	O2—C10—C14	123.10 (15)
C1—C2—H2A	110.4	C14—C10—C1	116.36 (14)
C1—C2—H2B	110.4	C10—C14—H14A	109.5
H2A—C2—H2B	108.6	C10—C14—H14B	109.5
C3—C2—C1	106.65 (13)	C10—C14—H14C	109.5
C3—C2—H2A	110.4	H14A—C14—H14B	109.5
C3—C2—H2B	110.4	H14A—C14—H14C	109.5
O1—C3—C2	113.49 (14)	H14B—C14—H14C	109.5
O1—C3—H3	108.8	C4—C15—H15A	109.5
O1—C3—C4	112.30 (14)	C4—C15—H15B	109.5
C2—C3—H3	108.8	C4—C15—H15C	109.5
C4—C3—C2	104.63 (13)	H15A—C15—H15B	109.5
C4—C3—H3	108.8	H15A—C15—H15C	109.5
C5—C4—C3	110.86 (14)	H15B—C15—H15C	109.5
C5—C4—C15	127.82 (16)		

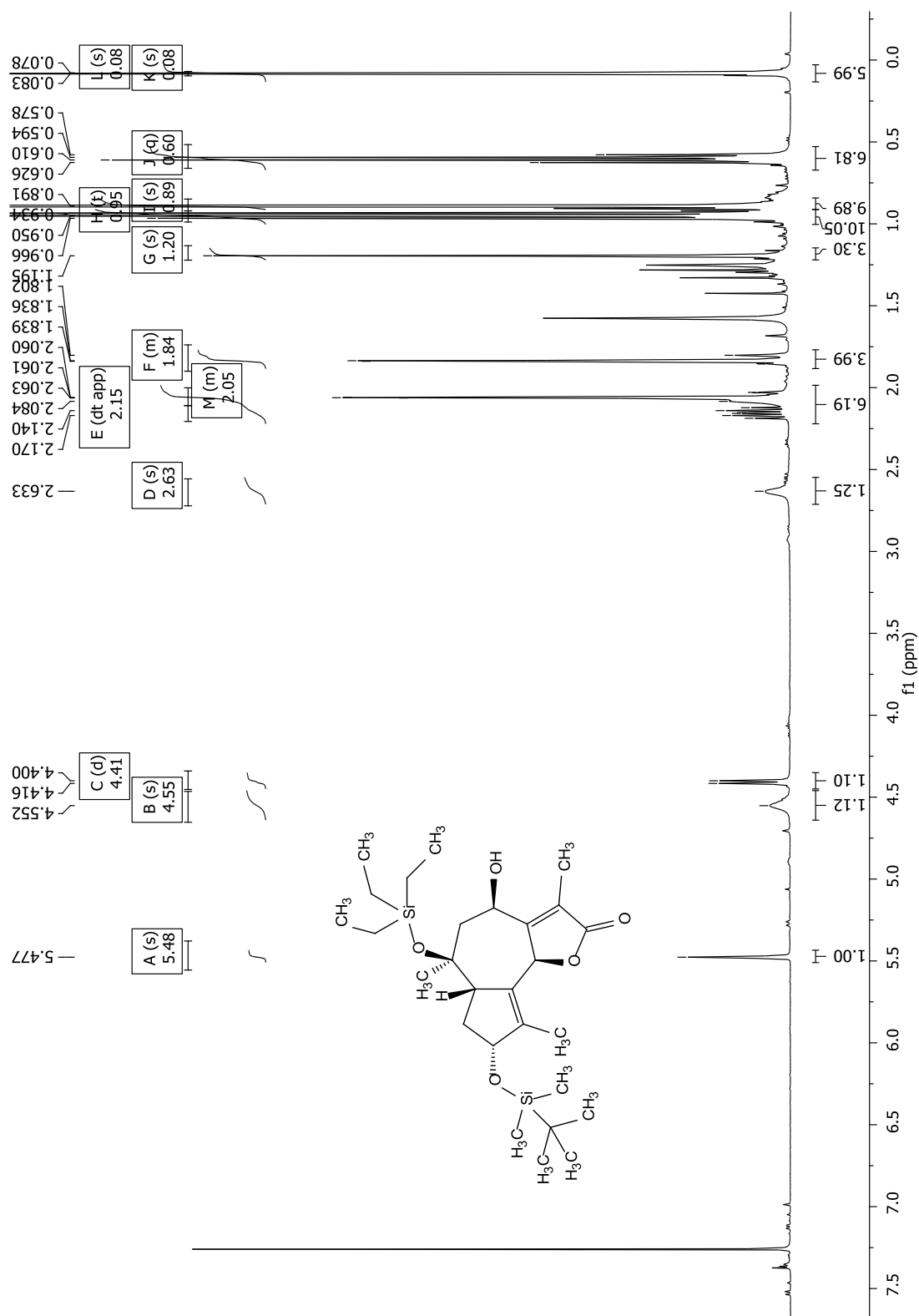
Hydrogen-bond geometry (Å, °)

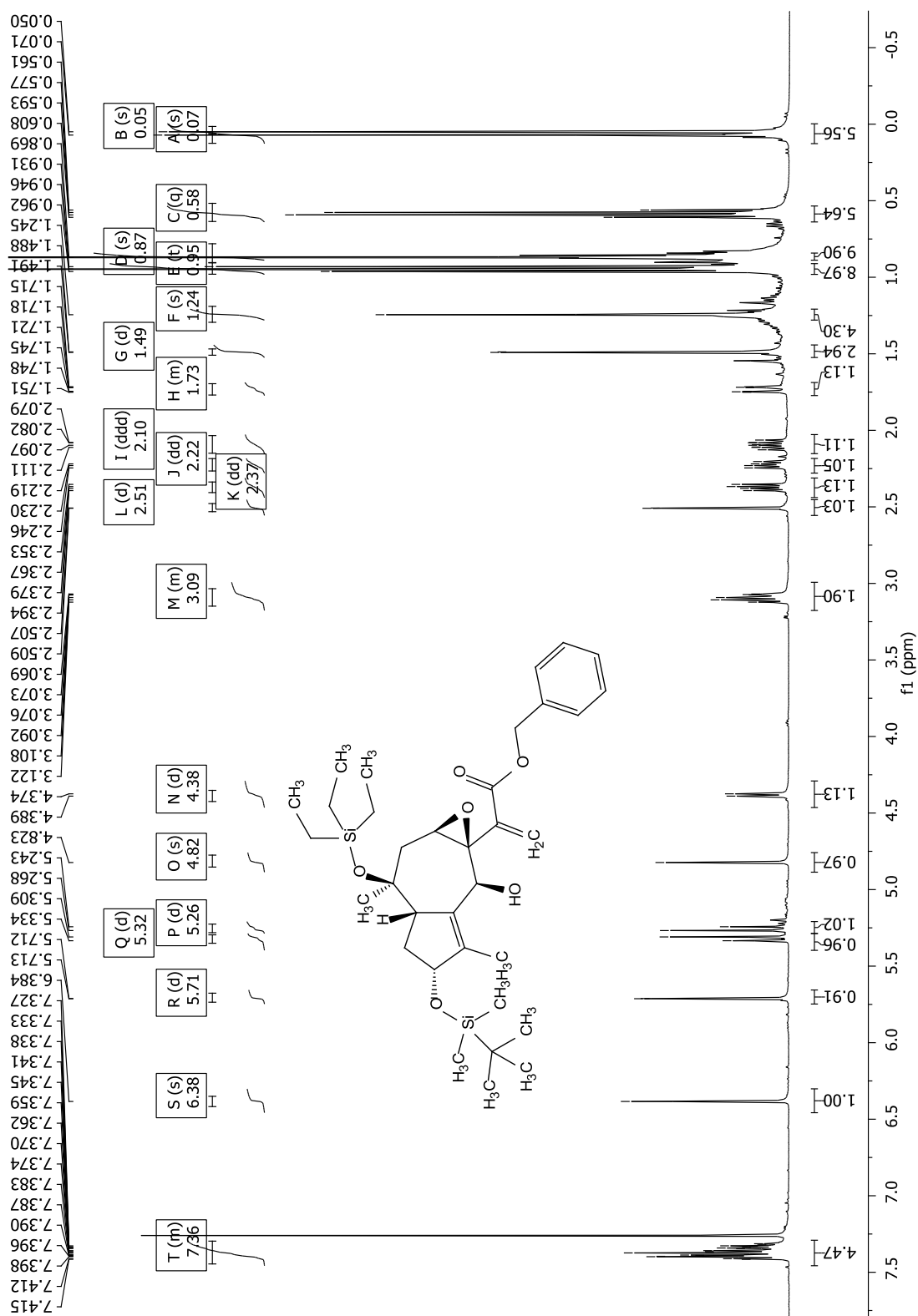
<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
O1—H1 \cdots O2 ⁱ	0.84	2.01	2.8358 (17)	166
C1—H1A \cdots O1 ⁱⁱ	1.00	2.60	3.447 (2)	142

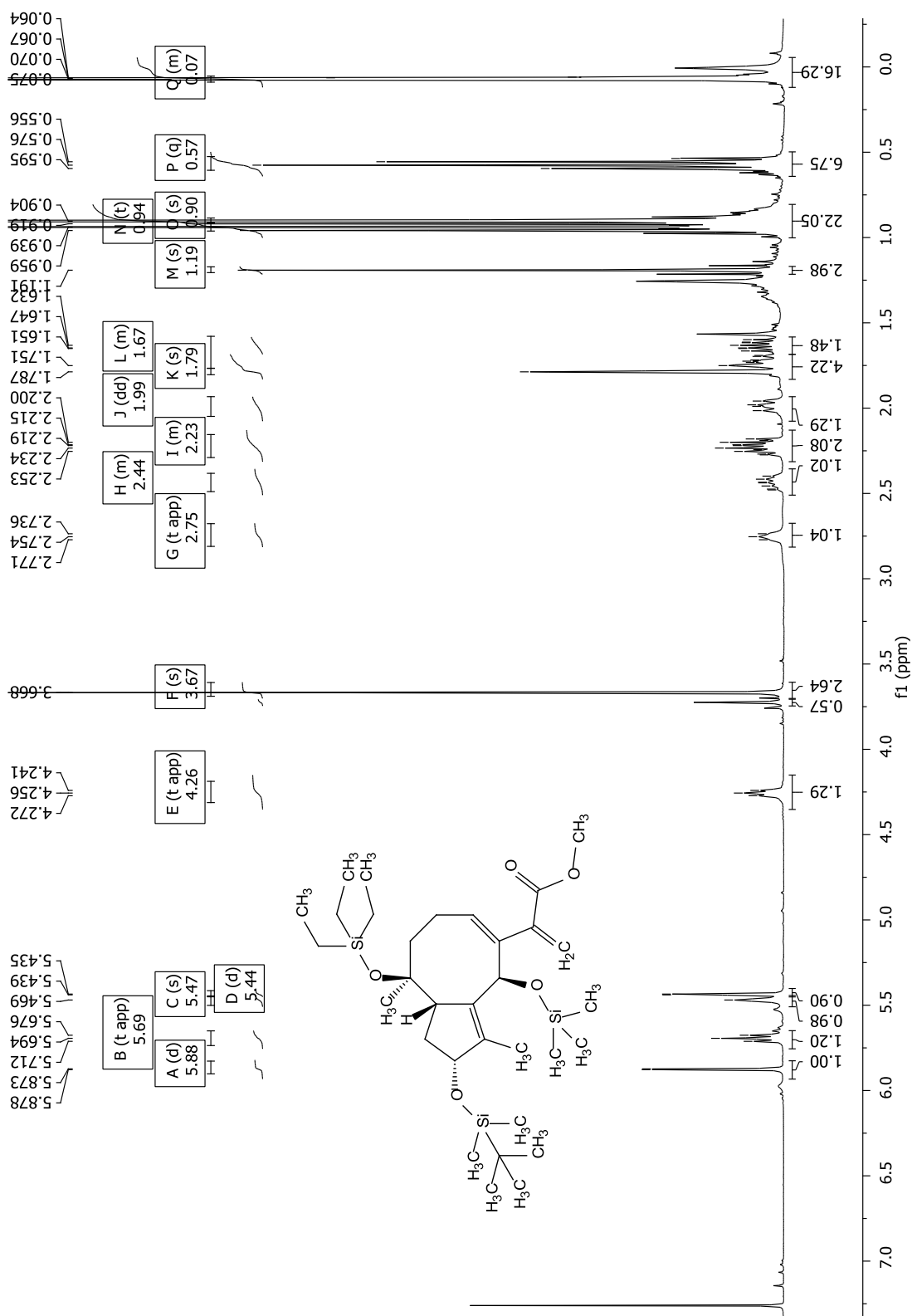
Symmetry codes: (i) $x+1/2, -y+3/2, -z+1$; (ii) $x-1, y, z$.

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Appendix B

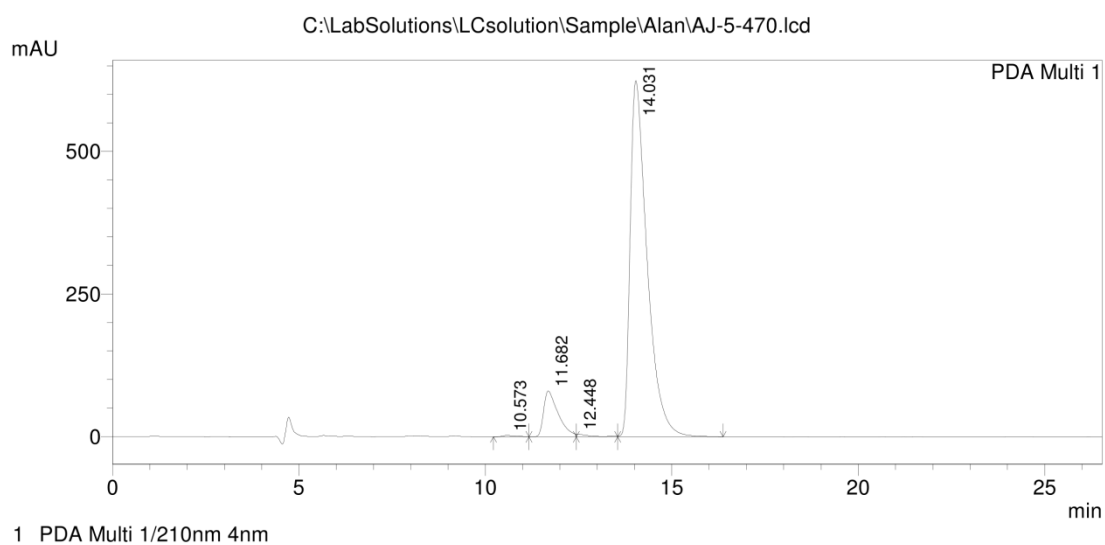






Appendix C

C:\LabSolutions\LCsolution\Sample\Alan\AJ-5-470.lcd
 Acquired by : Admin
 Sample Name : measure
 Sample ID : AJ-5-470-12%iPrOH
 Injection Volume : 20 uL
 Data File Name : AJ-5-470.lcd
 Method File Name : 15%iPrOH-0.7mLh-Alan.lcm
 Data Acquired : 04/12/2017 11:53:53
 Data Processed : 04/12/2017 12:20:27
 12% iPrOH in hex
 ADH Column
 0.5mL/h
 0.5mL/h
 0.5mL/h



PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.573	61024	2229	0.276	0.313
2	11.682	2169780	80283	9.825	11.284
3	12.448	105866	4623	0.479	0.650
4	14.031	19748505	624365	89.420	87.753
Total		22085175	711499	100.000	100.000